Glucocorticoids and Dopamine-1 Receptors on Vascular Smooth Muscle Cells

Kenichi Yasunari, Masakazu Kohno, Anthony Balmforth, Koh-ichi Murakawa, Koji Yokokawa, Naotsugu Kurihara, and Tadanao Takeda

The effect of glucocorticoids on the dopamine (DA)-mediated cyclic adenosine monophosphate (cAMP) by intact vascular smooth muscle cells (VSMC) was studied in rats. Cultured VSMC were obtained from renal arteries of 14-week-old Wistar-Kyoto rats by explant method. Micromolar concentrations of dexamethasone (DEX) pretreatment for 48 hours potentiated DA-mediated response without any change of affinity constant. However, micromolar concentrations of aldosterone pretreatment for 48 hours had almost no effect on DA-mediated response. The DEX-induced facilitation began at 6 hours and reached maximum at 24 hours after DEX administration in a dose-dependent manner. Inhibitors of protein and RNA synthesis blocked this glucocorticoid effect. The basal activity of adenylate cyclase in DEX-treated cells was twofold higher than that in control cells. Treatment of VSMC with DEX increased cholera toxin-stimulated and forskolin-stimulated adenylate cyclase activity. However, pertussis toxin treatment did not augment or reduce the effect of DEX treatment. These results suggest that glucocorticoids increase DA-mediated cAMP formation by VSMC through glucocorticoid type II receptors and the induction of protein synthesis and that the activation of the catalytic unit may play some role in this facilitation. (Hypertension 1989;13:575-581)

It has been shown that dopamine (DA) receptors in central nervous tissues can be separated into those that stimulate adenylate cyclase and those that inhibit the activity of the enzyme. They are designated D₁ receptors and D₂ receptors, respectively.¹ Two subtypes of DA receptor in peripheral tissues have also been suggested. They are designated DA₁ and DA₂ receptors.² The DA₁ receptor is situated postjunctionally on vascular smooth muscle,³ whereas the DA₂ receptor is situated prejunctionally on sympathetic nerve terminals.⁴ To study whether central D₁ and peripheral DA₁ receptors have similar biochemical characteristics, DA₁ receptors on the vascular smooth muscle cells (VSMC) from renal arteries (RA) in rats are evaluated by measuring cyclic adenosine monophosphate (cAMP) in this study.

The interaction of glucocorticoids with the cardiovascular system has been shown to play an important role in cardiovascular function. For example, glucocorticoid excess in the rat induces a rapid increase in blood pressure.⁵ Although it has been reported that glucocorticoids potentiate the response of vascular smooth muscle to the pressor effects of catecholamines,⁶,⁷ little is known about the molecular mechanisms whereby glucocorticoids affect the blood pressure and the vascular system. Consistent with the possibility of direct glucocorticoid effects, classical dexamethasone-binding glucocorticoid receptors in VSMC have been recently demonstrated.⁸,⁹ And glucocorticoid-induced hypertension is likely to involve the direct effect of glucocorticoid on vascular receptors.¹⁰ Glucocorticoids are known to enhance hormone stimulation of cAMP accumulation in many cell types.¹¹ The mechanism of this effect has not been fully elucidated and may vary among cells of different tissues. We have already reported that central D₁ receptors are regulated by glucocorticoid.¹² So far, there is no study on the interaction of glucocorticoid and DA₁ receptors at the cellular level. In the present study, the effects of glucocorticoids on the DA₁ receptors on VSMC from RA of Wistar-Kyoto (WKY) rats and the possible mechanisms of this interaction were studied.

Materials and Methods

Materials

- Type II collagenase, dexamethasone, aldosterone, 3-isobutyl-1-methylxanthine (IBMX), L-isoproterenol
HCl (Iso), DL-propranolol, 5-hydroxytryptamine (dopamine), choler toxin, cycloheximide, and actinomycin D were purchased from Sigma Chemical Co. (St. Louis, Missouri). Pertussis toxin (islet-activating protein) was purchased from Kaken Seiyaku Co. (Tokyo, Japan). Dulbecco's Modified Eagle Medium (DMEM), penicillin-streptomycin, trypsin, EDTA (Versene), and fetal calf serum (FCS) were purchased from Gibco Laboratories (Grand Island, New York). \(^{[4]}\text{C}\)cAMP and \(^{[3]}\text{H}\)adenine were purchased from Amersham Japan Co. (Tokyo, Japan). Multiwell plates, pipettes, and flasks were purchased from Becton, Dickinson and Co. (Oxnard, California). Anion exchange chromatography Dowex 50W-X4 and neutral alumina were purchased from Bio-Rad Laboratories (Richmond, California). SCH23390 was provided as a gift by Schering Co. (Bloomfield, New Jersey), domperidone by Kyowa Hakko Co. (Tokyo, Japan), and forskolin by Nihon Kayaku Co. (Tokyo, Japan).

**Isolation and Culture of Cells**

VSMC were isolated from the RA of 14-week-old WKY rats and were cultured according to the modification of the explant method of Ross. All procedures of animal handling were in accordance with guidelines of the Animal Research Committee of Osaka University Medical School. With the rats under pentobarbital anesthesia, RA were dissected free of surrounding tissues and placed in a 35-mm culture dish containing DMEM. The adventitious adipose tissues around the arteries were gently removed with forceps, and the arterial tissues were incubated for 10-20 minutes at 30°C in DMEM containing collagenase II (1 mg/ml). After incubation, vascular tissues were cut into small pieces and placed in 50-ml culture flasks with 5 ml DMEM containing 10% FCS. After sufficient immunoisolation of the cells, cells were subcultured by treatment with EDTA (Versene) followed by trypsin. Morphological examination of confluent cultures revealed characteristics of VSMC with crisscross patterns, hillock and valley, and nodular structures by phase-contrast microscopy and revealed myofilaments and dense bodies by electron microscopy. Cells at passage levels 3-9 were used for the experiments.

**Assay for Cyclic Adenosine Monophosphate Formation in Intact Cells**

Receptor-mediated cAMP formation was measured by prelabeling technique. All experiments with VSMC were conducted at least in triplicate by using six-well culture plates. Cells were preincubated with \(^{[3]}\text{H}\)adenine (2 µCi/ml) at 37°C for 2 hours. Before incubation, cells were rinsed three times with 2 ml DMEM. In most of the experiments, cells were incubated with agonist in 2 ml DMEM in the presence of the phosphodiesterase inhibitor IBMX 0.5 mM at 37°C in an atmosphere of 5% CO₂ and 95% air. Stimulation of the labeled cells was stopped by the addition of 1.5 ml 5% (wt/vol) ice-cold trichloroacetic acid (TCA) containing \(^{[3]}\text{H}\)cAMP as the internal standard. In some experiments, the culture medium was replaced by DMEM with 10% FCS containing DEX, aldosterone, or its vehicle (ethanol) 48 hours before the stimulation. TCA extracts were submitted to sequential ion exchange Dowex 50W-X4 and neutral alumina column chromatography for the isolation of \(^{[3]}\text{H}\)cAMP. Radioactivity was determined by liquid scintillation counting; samples were corrected for counting efficiencies by the external standard ratio technique and for the recovery of \(^{[3]}\text{H}\)cAMP (60-80%). Cells were counted with the use of an electronic cell counter (model Zf, Coulter Elec., Inc., Hialeah, Florida).

**Statistics**

Statistical analysis was performed by analysis of variance (ANOVA) and Scheffe's modified t test. Values of \(p<0.05\) were considered significant.

**Results**

**Evidence That Dopamine-Mediated Cyclic Adenosine Monophosphate Formation is DA₁ Specific**

DA stimulated adenylate cyclase in intact VSMC from RA from WKY rats. DA (10 µM)-mediated cAMP formation, which was not inhibited by propranolol (1 µM); its concentration was enough to block 10 µM isoproterenol-mediated cAMP formation completely (data not shown). However, in the presence of propranolol, the DA-mediated cAMP formation was completely blocked by SCH23390 (1 µM), a DA₁-specific dopamine antagonist, and was not blocked by domperidone (1 µM), a DA₂-specific dopamine antagonist (Figure 1).

**Effects of Glucocorticoid on Dopamine-Mediated Cyclic Adenosine Monophosphate Formation by Vascular Smooth Muscle Cells from Renal Arteries**

Incubation of VSMC from RA for 48 hours in the presence of DEX resulted in an increase in DA-mediated \(^{[3]}\text{H}\)cAMP formation by intact cells. The dose-response curves for DA in DEX-treated cells showed an increased maximum response that ranged generally from 350% to 380% above those of untreated cells, with no change in \(Kₐ\) values (agonist concentration producing half maximal stimulation). In comparison, aldosterone had almost no effect on the dose—response curves for DA (Figure 2).

Incubation of cells with DEX for various periods of time before DA stimulation of cAMP resulted in a detectable effect at 6 hours with a maximum effect at 24 hours. This effect was maintained for up to 72 hours, the longest time point studied (Figure 3).
Cells treated with different concentration of DEX exhibited a dose-related increase in the cAMP formation induced by DA (Figure 4).

Effects of Inhibitors of Protein Synthesis and RNA Synthesis on the Dexamethasone-Mediated Facilitation of the Dopamine Response

Steroid hormones act through interactions with specific cytosolic receptors that are translocated to the nuclei. To determine whether glucocorticoids were acting through a similar mechanism of action in VSMC from RA, we incubated cells with either cycloheximide 30 μM or actinomycin D 5 μg/ml in the presence or absence of DEX for 48 hours. Both inhibitors completely abolished the response to DEX without altering ability of the cell to respond to DA (Table 1).

Effect of Dexamethasone Treatment on Stimulatory and Inhibitory Guanine Nucleotide-Binding Proteins

To evaluate possible changes in the stimulatory guanine nucleotide–binding protein (G\textsubscript{s}) cells were treated with cholera toxin, 0.3 μg/ml for 1 hour, which causes a permanent activation of adenylate cyclase via G\textsubscript{s} nicotinamide adenine dinucleotide–dependent adenosine diphosphate ribosylation.\textsuperscript{17,18} Cholera toxin stimulation of cAMP formation was enhanced approximately threefold by DEX treatment in this case. Hormone stimulation in the presence of DEX was four to six times higher (Table 2). To examine the roles of the inhibitory guanine nucleotide–binding protein (G\textsubscript{i}) in the DEX enhancement of adenylate cyclase stimulation, cells were treated with pertussis toxin 100 ng/ml for 3 hours, which blocks the action of G\textsubscript{i}.\textsuperscript{19} Pertussis toxin treatment had no effect on cAMP accumulation in these cells in the presence of DA. DEX treatment for 48 hours neither abolished nor augmented the pertussis toxin effect (Table 3).

Effect of Dexamethasone Treatment on the Catalytic Unit

To study the role of the catalytic unit in the DEX enhancement of adenylate cyclase stimulation, cells were stimulated with forskolin, which directly activates the catalytic unit of adenylate cyclase.\textsuperscript{20} DEX treatment for 48 hours potentiates forskolin-mediated cAMP formation by VSMC from the RA of WKY rats (Figure 5).

Discussion

DA has a direct vasodilator action on renal vascular beds.\textsuperscript{1} The vasodilator action of DA is considered to be due to DA\textsubscript{1} receptors.\textsuperscript{2} Like other vasodilator agents such as prostaglandin E and isoproterenol, this vasodilator action can be due to increased intracellular cAMP, which activates cAMP-dependent protein kinase and myosin kinase and leads to the suppression of intracellular ionized calcium elevation.\textsuperscript{21}
In general, the DA₁ and DA₂ classification has been used to distinguish between the peripheral effects of DA determined by physiological methods, such as in vivo administration, whereas the D₁ and D₂ classification has been developed on the basis of biochemical techniques. The results of this investigation indicate that DA increases cAMP in VSMC and that this effect is blocked by SCH23390, not by domperidone; therefore, the evidence indicates that DA₁ receptor activity can be measured by D₁ receptors that are similar to cAMP. However, although SCH23390 is commonly described as a DA₁-specific antagonist, it also blocks other receptors. So we cannot completely rule out the contribution of other receptors. We have reported that central D₂ receptor was measured by cAMP formation by human astrocytoma clone. The similarities of the biochemical responses to stimulation of peripheral DA₁ receptors and central D₂ receptors are: 1) Dopamine stimulation occurred in a concentration-dependent manner. 2) Kᵣ, apparent values (agonist concentration producing half-maximal stimulation) are in micromolar order. 3) The DA₁ and D₁-selective antagonist SCH23390 10⁻⁶ M inhibited 10⁻⁵ M DA-induced cAMP formation.

Our studies have shown that glucocorticoid increases DA₁ receptor-mediated cAMP formation by VSMC from RA of WKY rats. The dose-response curve to DEX and the fact that aldosterone had almost no effect on the DA dose-response curve suggest that this action is mediated through glucocorticoid type II receptors. The time course for glucocorticoid action, as well as the fact that RNA and protein synthesis inhibitors blocked the effect, strongly supports the involvement of a genomic mechanism of action and the requirement for de novo protein synthesis. This behavior is consistent with the general mode of action of steroid hormones. However, like all cycloheximide and actinomycin D data, these data should be interpreted with caution since the synthesis of other proteins, including, possibly, the glucocorticoid receptor itself, could be inhibited at the same time.

The glucocorticoid enhancement of hormone-stimulated cAMP accumulation has been reported in many cell types. In astrocytoma cells, glucocorticoids increase the number of β-adrenergic receptors. In fibroblasts, there is an increase in guanosine triphosphate (GTP)-stimulated adenylate cyclase activity, suggesting a change in the Gₛ or in the catalytic unit itself. Glucocorticoids also...
alter the GTP-dependent reduction in receptor (apparent) affinity for isoproterenol. This alteration suggests changes in the coupling of receptors to \( G_i \).

No data on the participation of \( G_i \) in glucocorticoid action have been reported. A reduction in phosphodiesterase activity was shown to occur in fibroblasts and other cells. 31-34

We have demonstrated in this study that DEX increases basal and DA-stimulated cAMP formation by VSMC from RA. Previously we (unpublished observation) and others 29 have observed that DEX also increases \( \beta \)-adrenergic receptor– and prostaglandin \( E_2 \), receptor–mediated cAMP formation. 15

Although different mechanisms may underlie these augmented responses by DEX, there is a possibility that common mechanisms such as reduction in phosphodiesterase activity, rise in enzyme abundance, increase in receptor number, \( G_i \) abundance and function, and adenylate cyclase catalytic unit activity may contribute to this facilitation.

The potentiation by DEX of the DA-induced cAMP formation might be due to decrease in phosphodiesterase activity. However, data suggest that, in this case, the effect of dexamethasone is at the level of adenylate cyclase rather than at the level of phosphodiesterase since, as previously reported, 35 the potentiation occurred in the presence of the phosphodiesterase inhibitor IBMX.

The increase in adenylate cyclase activity in the absence of stimulating agents suggests a rise in enzyme abundance; however, no means are currently available to directly investigate this finding. Although glucocorticoid increases \( \beta \)-receptor number in many tissues, 11 there is a study showing no change in the prostaglandin \( E_2 \), receptor number. 36

The contribution of the functional increase in \( G_i \), observed after cholera toxin–stimulated cAMP accumulation in increased hormone stimulation, is hard to estimate since it could not be separated from the change in receptor abundance or receptor number. A recent study 37 shows direct evidence of glucocorticoid effects on \( G_i \) levels in osteosarcoma cells. Therefore, \( G_i \) protein might play some role in this facilitation.

The effect of pertussis toxin was also examined in prostaglandin \( E_2 \),–mediated cAMP formation by VSMC. 35 Concentration and incubation time of pertussis toxin were completely the same as in the present study, and pertussis toxin treatment was done at the same time. Although no differences were observed with pertussis toxin treatment alone, pertussis toxin significantly increased prostaglandin \( E_2 \)–induced cAMP formation (105,400±1,600 vs. 120,800±2,500 dpm/10^6 cells, significant by ANOVA and Scheffe’s modified test). In the present study, DEX-induced facilitation of DA-mediated hormone stimulation was not altered by pertussis toxin treatment. This finding indicates that DA\(_i\) receptors might not be \( G_i \) linked, although further study will be necessary to conclude this.

The activation of the catalytic unit (forskolin stimulation) increased the specific activity of the enzyme in parallel to the basal activity in DEX-treated cells. These results may suggest that glucocorticoids are acting at a site beyond the receptor. Since activation of adenylate cyclase by forskolin is

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**Table 1. Effect of Inhibitors of Protein Synthesis and RNA Synthesis on the Dexamethasone-Mediated Facilitation of the Dopamine Response**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Cyclic [3H]AMP (dpm/10^6 cells)</th>
<th>Fold increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>DEX (1 ( \mu )M)</td>
</tr>
<tr>
<td>None</td>
<td>14,900±2,100</td>
<td>49,800±700</td>
</tr>
<tr>
<td>Cycloheximide</td>
<td>10,700±900</td>
<td>10,700±900</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>9,800±4,000</td>
<td>9,900±900</td>
</tr>
</tbody>
</table>

Vascular smooth muscle cells were incubated with 1 \( \mu \)M dexamethasone (DEX) or its vehicle (control) for 48 hours. After incubation with cholera toxin (ChT) 0.3 \( \mu \)g/ml or its vehicle (control) for 1 hour, cells were stimulated with dopamine (DA) (10 \( \mu \)M). Results were expressed as mean±SD from two independent experiments done in triplicate. AMP, adenosine monophosphate.

*p<0.05 compared with control.

**Table 2. Effect of Cholera Toxin on the Dexamethasone-Mediated Facilitation of Dopamine Response by Vascular Smooth Muscle Cells From Renal Arteries**

<table>
<thead>
<tr>
<th>DA</th>
<th>Cyclic [3H]AMP (dpm/10^6 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Basal</td>
<td>2,800±500</td>
</tr>
<tr>
<td>DA</td>
<td>22,300±1,800</td>
</tr>
<tr>
<td>ChT</td>
<td>59,700±6,700</td>
</tr>
<tr>
<td>ChT+DA</td>
<td>81,900±4,300</td>
</tr>
</tbody>
</table>

Vascular smooth muscle cells were preincubated with 1 \( \mu \)M dexamethasone (DEX) or its vehicle (control) for 48 hours. After incubation with cholera toxin (ChT) 0.3 \( \mu \)g/ml or its vehicle (control) for 1 hour, cells were stimulated with dopamine (DA) (10 \( \mu \)M). Results were expressed as mean±SD from two independent experiments done in triplicate. AMP, adenosine monophosphate.

*p<0.05 compared with control.

**Table 3. Effect of Pertussis Toxin on the Dexamethasone-Mediated Facilitation of Dopamine Response by Vascular Smooth Muscle Cells From Renal Arteries**

<table>
<thead>
<tr>
<th>DA</th>
<th>Cyclic [3H]AMP (dpm/10^6 cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Basal</td>
<td>1,700±400</td>
</tr>
<tr>
<td>DA</td>
<td>35,500±2,800</td>
</tr>
<tr>
<td>PT</td>
<td>1,600±400</td>
</tr>
<tr>
<td>PT+DA</td>
<td>35,200±700</td>
</tr>
</tbody>
</table>

Vascular smooth muscle cells were preincubated with 1 \( \mu \)M dexamethasone (DEX) or its vehicle (control) for 48 hours. After incubation with pertussis toxin (PT) 100 ng/ml or its vehicle (control) for 3 hours, cells were stimulated with dopamine (DA) (10 \( \mu \)M). Results were expressed mean±SD from two independent experiments done in triplicate. AMP, adenosine monophosphate; NS, not significant.

*p<0.05 compared with control.

*p<0.05.
commonly thought to be mediated primarily by a direct action on the catalytic unit, the most obvious interpretation of these results is that glucocorticoid actions are exerted at the level of the catalytic unit of adenylate cyclase.

The effects of glucocorticoids on DA-mediated cAMP formation may also reflect increased receptor availability for binding due to changes in membrane lipid metabolism. These effects have been reported, and alterations in membrane lipid can modify receptor binding and adenylate cyclase activity.

The physiological significance of these facilitations of receptor response remains to be elucidated. It has been reported that glucocorticoids potentiate the vasoconstrictor response to norepinephrine and epinephrine in experimental animals. Since DA, dopaminergic receptors on VSMC are thought to induce vasodilation, there is a discrepancy between these two findings. The fact that glucocorticoid-enhanced, DA-induced cAMP production on VSMC also provides the molecular basis of glucocorticoids and dopamine combination therapy to preserve renal blood flow after shock.

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