EFFECTS OF GLUCAGON ON THE RENAL HEMODYNAMICS IN THE DOG

Juro Ueda, Hitoshi Nakanishi, Mizuo Miyazaki*, and Youichi Abe*

The effect of glucagon on the renal hemodynamics in the dog was examined by comparing its effect with that of secretin, a peptide with which glucagon shares a similar chemical structure. An intrarenal infusion of glucagon resulted in increases of RBF and GFR. GFR rose by approximately the same order of magnitude of RBF. The increase in GFR depended on the selective dilation of the afferent arteriole and a consequent rise in the transcapillary pressure difference. On the other hand, secretin infusion produced highly significant and proportional decreases in both afferent and efferent arteriolar resistance, resulting in no change in GFR.

A superimposition of acetylcholine to glucagon decreased GFR even though RBF increased significantly. Glucagon infusion did not affect the permeability of glomerular capillary and the distribution of cortical blood flow. These findings indicate that the effect of glucagon on GFR depended on the selective dilation of afferent arteriole, and that as a result of its dilation the net filtration pressure increased without any change in permeability of glomerular capillary and a redistribution of filtration.

GLUCAGON, the polypeptide humoral substance produced mainly by the alpha cells of the pancreas, is generally considered to act as a glycogenolytic hormone. In addition to that action, recent studies have demonstrated that small intravenous doses of glucagon may cause marked increases in renal blood flow (RBF) and glomerular filtration rate (GFR) in dogs.1-4 This response was independent of the hyperglycemic action of glucagon or of the increased cardiac output.1-3,5 Like glucagon, a small dose of secretin, a peptide with which glucagon shares a similar chemical structure, also produced an increase in RBF, but with no effect on GFR.6

In general, the vasodilating agents such as acetylcholine, bradykinin and prostaglandins are capable of producing marked alterations in RBF without affecting GFR.7-9 There are many factors which regulate GFR.10 The driving force for the formation of an ultrafiltrate of plasma is the difference between the glomerular capillary hydrostatic pressure and the pressure in Bowmian’s space which is determined by the relative tonus of two renal resistance vessels: afferent arteriole and efferent arteriole.

In the present study, the effects of glucagon on RBF, GFR and afferent and efferent arteriolar resistance were examined by comparing its effects with those of secretin in the anesthetized dogs. In addition, since two types of nephron possessing the different single nephron GFR were distributed in the renal cortex,11 the effects

Key Words:
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Secretin
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of glucagon on intrarenal hemodynamics were also examined.

MATERIALS AND METHODS

Mongrel dogs weighing 12–17 kg were anesthetized with pentobarbital sodium (30 mg/kg, i.v.) and were then given additional doses as required during the experiment. The left kidney was exposed through a retroperitoneal flank incision. The kidney was denervated by division of all visible nerve fibers and sharp dissection of tissue connected to the renal hilum cephalad to the renal artery. RBF was measured by an electromagnetic flowmeter (Nihonkoden MF-26). Renal arterial pressure was considered equal to the aortic pressure measured at the level of the renal artery. Systemic arterial blood was collected from the right brachial artery, and the renal venous blood was collected via a cannula introduced through the left spermatic or ovarian vein. A polyethylene tube was inserted into the left ureter and urine was collected throughout the experiment.

An intravenous infusion of 0.9% saline, 4.0 ml/min, was started after anesthesia. A no. 23-gauge needle was introduced into the left renal artery proximal to the flow probe for infusion of saline or drug solution at a rate of 0.5 ml/min. A loading dose of creatinine (100 mg/kg) was given intravenously, followed by a maintenance dose of 50 mg/kg per hour. GFR was measured by creatinine clearance. At reduced pressures in group 3) experiment, GFR was calculated as follows: GFR = (systemic arterial concentration of creatinine - renal venous concentration of creatinine) x renal plasma flow/systemic arterial concentration of creatinine.

The experiments were divided into the following four groups.

1) The effects of glucagon and secretin on RBF and GFR were evaluated in 15 dogs. Three 10 min urine collections with arterial blood sample withdrawn at the midpoint of each period were taken as control. Glucagon or secretin was then infused into the renal artery for 30 min. Both blood and urine samples were taken at 10, 20 and 30 min during glucagon or secretin infusion. After cessation of drugs, three more samples were obtained at 10, 20 and 30 min. The changes in afferent and efferent arteriolar resistance were calculated by the formula which was previously reported.

2) In 5 dogs, 15 min after the administration of glucagon (0.5 µg/kg/min), acetylcholine was superimposed into the renal artery at a rate of 4.0 µg/kg.min for 20 min. Both blood and urine samples were collected and then GFR was calculated.

3) The effect of glucagon (0.5 µg/kg.min) on the permeability coefficient of glomerular capillary was examined in 4 dogs. During control the permeability coefficient was calculated by the formula using GFR and RBF measured at 2 points of renal arterial pressure below the autoregulatory range (75, 50 mmHg) since the efferent arteriolar resistance might be constant below the range of autoregulation. The same procedures were repeated during the intrarenal infusion of glucagon. Then the permeability coefficients at control and at glucagon infusion were compared.

4) The effect of glucagon (0.5 µg/kg.min) on the intrarenal hemodynamics was examined in 8 dogs. Microsphere injections were performed before and 15 min after glucagon infusion, respectively.

Drugs used in the present study were glucagon (glucagon Novo, Novo Ind.) and porcine secretin (Eisai Co.) which possesses equipotency with Boots secretin in increasing the pancreatic secretion.

ANALYTICAL PROCEDURES

Distribution of cortical blood flow was determined with radioactive microspheres (3M Company, St. Paul, Minn, U.S.A.) by the technique described in a previous paper. The renal cortex was cut parallel to the surface into four zones of equal thickness. Four cortex zones were analyzed for individual isotope counts, and the perfusion rate of each zone was calculated. The volume of each cortex zone was approximated by calculations based on the formula for an ellipsoid. The volume of the individual cortex zone, expressed as percent of total renal volume, was: zone 1), 27.0, zone 2), 21.9, zone 3), 17.3, zone 4), 12.2.

The segmental renal vascular resistance was calculated by the following formula.

According to the concepts of glomerular dynamics:

\[ GFR = \lambda (P_g - P_t - P_o) \]  

i.e., GFR is proportional to the effective filtration pressure; \( \lambda \) is the permeability coefficient related to the area and permeability of the glomerular capillary wall.

\( P_t \): tissue pressure

\( P_o \): mean glomerular capillary plasma

onctic pressure
Now, the efferent arteriolar resistance (Re)
\[ \text{Re} = \frac{(\text{Pg} - \text{Pt})}{\text{RBF}} \]

Rearrangement of the relationship yields:
\[ (\text{Pg} - \text{Pt}) = \text{Re} \times \text{RBF} \]

Substituting equation (3) into (1), we obtain:
\[ \text{GFR} = \lambda (\text{Re} \times \text{RBF} - \text{Po}) \]
\[ \text{Re} = \left( \frac{\text{GFR}}{\lambda + \text{Po}} \right) / \text{RBF} \]

In this expression, only \( \lambda \) is not directly known. We have previously reported that the mean value of \( \lambda \) in the dog kidney was 0.0196 ± 0.0023 ml/mmHg.min. In the present experiment, this mean value, 0.0196 ml/mmHg.min was used to calculate Re and afferent arteriolar resistance (Ra).
\[ \text{RT} = \text{Ra} + \text{Re} + \text{Rav} \]
\[ \text{RT} : \text{total vascular resistance} \]
\[ \text{Rav: arcuate venous resistance} \]
\[ = 3.53 \pm 0.06 \text{mmHg.g.min/ml} \]
\[ \text{Ra} = \text{RT} - \text{Re} - 3.53 \]

Since RT is known from RBF and blood pressure, Ra is readily calculated with the above equation.

The mean and standard error of significance was determined by Student’s paired and nonpaired t-test.

RESULTS
1) Effects of glucagon and secretin on RBF, GFR and segmental renal vascular resistance.

Intrarenal infusion of glucagon at doses of 0.01, 0.1 and 0.5 \( \mu \text{g/kg.min} \) resulted in the dose dependent increases of RBF and GFR without any change of systemic arterial pressure. RBF gradually increased and reached its maximum 10–20 min after infusion at each dose. GFR also showed the same response pattern (Table I). At 0.5 \( \mu \text{g/kg.min} \), RBF and GFR increased from 2.80 ± 0.24 and 0.58 ± 0.06 ml/g.min to 3.64 ± 0.31 and 0.78 ± 0.07 ml/g.min respectively (p < 0.05). Since the degrees of responses in RBF and GFR were almost same, the calculated filtration fraction was not affected by the glucagon infusion. Intrarenal infusion of secretin at doses of 0.2 and 1.0 unit/kg.min produced marked increases of RBF from 2.66 ± 0.14 and 2.53 ± 0.25 ml/g.min to 3.21 ± 0.21 and 4.05 ± 0.34 ml/g.min respectively (p < 0.05), but GFR keeps control values at both doses (Table I). Effects of glucagon and secretin on renal segmental resistances were showed in Fig. 1 and Table I.

Intrarenal infusion of glucagon (0.5 \( \mu \text{g/kg.min} \))

| TABLE I: EFFECTS OF GLUCAGON AND SECRETIN ON RBF, GFR AND SEGMENTAL VASCULAR RESISTANCE |
|---------------------------------|--------|--------|--------|--------|--------|--------|
|                                 | RAP mmHg | RBF ml/g.min | GFR ml/g.min | Rt | Ra mmHg.g.min/ml | Re |
| Control                        | 135 ± 7 | 2.95 ± 0.36 | 0.56 ± 0.10 | 50.2 ± 6.5 | 28.4 ± 5.2 | 18.2 ± 1.7 |
| Glucagon (0.01 \( \mu \text{g/kg.min} \)) | 132 ± 6 | 3.39 ± 0.39 | 0.69 ± 0.11 | 42.6 ± 5.4 | 21.3 ± 5.4 | 17.7 ± 1.4 |
| Control                        | 136 ± 7 | 3.57 ± 0.60 | 0.75 ± 0.08 | 42.5 ± 5.6 | 19.7 ± 3.8 | 19.3 ± 2.2 |
| Glucagon (0.1 \( \mu \text{g/kg.min} \)) | 132 ± 7 | 4.26 ± 0.61 | 0.97 ± 0.10 | 33.9 ± 4.2 | 11.7 ± 2.4 | 18.7 ± 2.2 |
| Control                        | 132 ± 5 | 2.28 ± 0.24 | 0.58 ± 0.06 | 49.7 ± 3.8 | 25.0 ± 1.8 | 21.1 ± 2.7 |
| Glucagon (0.5 \( \mu \text{g/kg.min} \)) | 125 ± 5 | *3.64 ± 0.31 | *0.78 ± 0.07 | **36.5 ± 3.2 | **13.4 ± 1.0 | 19.7 ± 2.9 |
| Control                        | 134 ± 5 | 2.66 ± 0.14 | 0.73 ± 0.08 | 50.8 ± 2.6 | 23.7 ± 3.0 | 23.5 ± 1.8 |
| Secretin (0.2 unit/kg.min)     | 134 ± 5 | *3.21 ± 0.21 | 0.72 ± 0.07 | 42.2 ± 2.5 | 18.8 ± 2.4 | 19.9 ± 1.7 |
| Control                        | 123 ± 4 | 2.53 ± 0.25 | 0.75 ± 0.07 | 50.3 ± 3.6 | 22.2 ± 2.6 | 24.1 ± 1.5 |
| Secretin (1.0 unit/kg.min)     | 121 ± 5 | **4.05 ± 0.34 | 0.78 ± 0.09 | 31.4 ± 1.2 | 10.3 ± 1.0 | 15.8 ± 0.7 |

All values are means ± S.E. *p < 0.05, **p < 0.01

Fig.1. Effects of the intrarenal arterial infusion of glucagon and secretin on the renal segmental vascular resistance, afferent arteriolar resistance (Ra) and efferent arteriolar resistance (Re). Each column represents the percent change from the control.

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>EFFECTS OF SUPERIMPOSED ACETYLCHOLINE TO GLUCAGON ON RBF, GFR AND SEGMENTAL VASCULAR RESISTANCE</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Segmental resistance</td>
</tr>
<tr>
<td></td>
<td>RAP mmHg</td>
</tr>
<tr>
<td>Control</td>
<td>129 ± 8</td>
</tr>
<tr>
<td>Glucagon (0.5 µg/kg·min)</td>
<td>121 ± 8</td>
</tr>
<tr>
<td>Glucagon (0.5 µg/kg·min)*</td>
<td>120 ± 8</td>
</tr>
<tr>
<td>Acetylcholine (4.0 µg/kg·min)</td>
<td>120 ± 8</td>
</tr>
</tbody>
</table>

All values are means ± S.E.
Comparison was made between interventions.
* p < 0.05, ** p < 0.01

resulted in a marked decrease of total vascular resistance from 49.7 ± 3.8 to 36.5 ± 3.2 mmHg·g·min/ml and its change was confined almost entirely to Ra, i.e., Ra decreased from 25.0 ± 1.0 to 13.4 ± 1.0 mmHg·g·min/ml, but Re was not changed. On the other hand, secretin infusion
TABLE III  EFFECTS OF GLUCAGON THE PERMEABILITY OF GLOMERULAR CAPILLARY

<table>
<thead>
<tr>
<th>No.</th>
<th>RAP (mmHg)</th>
<th>RBF (ml/g-min)</th>
<th>GFR (ml/g-min)</th>
<th>Calculated permeability coefficient (ml/mmHg-g-min)</th>
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<tbody>
<tr>
<td>1</td>
<td>89</td>
<td>2.17</td>
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<td>0.0163</td>
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<tr>
<td></td>
<td>54</td>
<td>1.57</td>
<td>0.18</td>
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<td>3</td>
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<td>0.0024</td>
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<td></td>
<td>60</td>
<td>0.91</td>
<td>0.11</td>
<td></td>
</tr>
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<td>4</td>
<td>65</td>
<td>1.92</td>
<td>0.26</td>
<td>0.0152</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>1.47</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

**Control**

Mean values ± S.E.

<table>
<thead>
<tr>
<th></th>
<th>RAP (mmHg)</th>
<th>RBF (ml/g-min)</th>
<th>GFR (ml/g-min)</th>
<th>Calculated permeability coefficient (ml/mmHg-g-min)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>82 ± 6</td>
<td>2.23 ± 0.12</td>
<td>0.37 ± 0.05</td>
<td>0.0097 ± 0.0035</td>
</tr>
<tr>
<td></td>
<td>53 ± 3</td>
<td>1.30 ± 0.14</td>
<td>0.14 ± 0.02</td>
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</tbody>
</table>

**Glucagon (0.5 μg/kg-min)**

Mean values ± S.E.

<table>
<thead>
<tr>
<th></th>
<th>RAP (mmHg)</th>
<th>RBF (ml/g-min)</th>
<th>GFR (ml/g-min)</th>
<th>Calculated permeability coefficient (ml/mmHg-g-min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>88</td>
<td>2.61</td>
<td>0.50</td>
<td>0.0114</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>1.69</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>2.68</td>
<td>0.70</td>
<td>0.0199</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>1.55</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>86</td>
<td>2.76</td>
<td>0.48</td>
<td>0.0040</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>1.37</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>1.56</td>
<td>0.31</td>
<td>0.0099</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>1.36</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

resulted in a same degree of reduction in total vascular resistance, accompanied by significant reductions in both Ra and Re.

2) Effects of superimposed acetylcholine to glucagon on RBF and GFR.

An additional infusion of acetylcholine at a rate of 4.0 μg/kg.min, which is an effectively maximum dose, to glucagon infusion (0.5 μg/kg-min) resulted in further increase in RBF from 3.71 ± 0.09 to 5.68 ± 0.71 ml/g.min and a decrease in GFR from 0.71 ± 0.09 to 5.3 ± 0.09 ml/g.min (Table II). Acetylcholine dilated both afferent and efferent arterioles, but a decrease in Re was larger than that in Ra.

3) Effect of glucagon on permeability coefficient of glomerular capillary.

The calculated permeability coefficient at control and at glucagon infusion were tabulated in Table III. The permeability coefficient within the nonautoregulatory range at control was 0.0097 ± 0.0035 ml/mmHg.g.min and the value during glucagon infusion was not significantly different from control value in the same dog. This indicated no effect of glucagon on the permeability of glomerular capillary.

4) Effects of glucagon on intrarenal hemodynamics.

The flow per gram of each cortex zone before and after glucagon infusion was presented in Fig. 2. At control, tissue perfusion rate of each zone differed significantly from that of the other three. The inner zones were characterized by the lower perfusion rates. The response to glucagon was characterized by an almost uniform increase in perfusion rates in all four cortex zones. The percents of total renal blood flow perfusing each cortex zone before and after glucagon infusion were presented in Table IV. It was evident that glucagon did not affect the distribution pattern.

**DISCUSSION**

In the present study, the effect of glucagon on
Fig. 2. Blood flow rates of individual cortex zones and whole kidney, and percent distribution to each zone before and after glucagon infusion at a rate of 0.5 μg/kg-min. Glucagon infusion resulted in an almost uniform increase in perfusion in all four cortex zones.

**TABLE IV EFFECT OF GLUCAGON ON THE PERCENT DISTRIBUTION OF BLOOD FLOW TO CORTEX ZONES**

<table>
<thead>
<tr>
<th></th>
<th>RAP</th>
<th>RBF</th>
<th>% distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>ml/g·min</td>
<td>C-1</td>
</tr>
<tr>
<td>Control</td>
<td>133 ± 3</td>
<td>2.61 ± 0.20</td>
<td>25.8 ± 1.7</td>
</tr>
<tr>
<td>Glucagon (0.5 μg/kg·min)</td>
<td>126 ± 4</td>
<td>*3.30 ± 0.24</td>
<td>25.0 ± 2.3</td>
</tr>
</tbody>
</table>

*All values are means ± S.E., *p < 0.05

the renal hemodynamics was examined by comparing its effect with that of secretin, a peptide with which glucagon shares similar chemical structure. Intrarenal infusion of glucagon resulted in increases of RBF and GFR. GFR rose by approximately the same order of magnitude of RBF. When secretin was infused into the renal artery, RBF increased, but GFR was not. In general, GFR is primarily determined by the mean transcapillary hydraulic pressure difference, which is thought to be altered by changes in either afferent or efferent arteriolar tone. For example, if a drug dilates selectively the afferent arteriole, thereby decreasing Rs, RBF will be raised with a consequent rise in transcapillary pressure difference. As a result of this rise in transcapillary pressure difference, GFR will also increase. Alternatively, if Rs is selectively reduced, the transcapillary pressure difference will reduce, even though RBF increases. As a result of fall in transcapillary pressure difference, GFR will decline. In the present study, the
segmental renal vascular resistance was calculated and the differential effects of glucagon and secretin were analysed.

An intrarenal infusion of glucagon produced a highly significant decrease in Ra but not in Re. Thus, glucagon caused dilation of the afferent arteriole, and RBF and GFR increased proportionally with a consequent rise in the transcapillary pressure difference. On the other hand, secretin infusion resulted in highly significant and proportional decreases in Ra and Re, and therefore GFR remained unchanged. This specific effect of glucagon on afferent arteriole was observed at doses of 0.01, 0.1 and 0.5 μg/kg.min., even though the level of flow response to glucagon was a match for that to secretin. This result indicates the difference in sensitivity to these two vasodilators between the afferent arteriole and the efferent arteriole.

Recently a high degree of dependence of GFR on renal plasma flow was reported. Brenner and colleagues\textsuperscript{16} demonstrated a direct relationship between renal plasma flow and GFR following vasodilation in the rat. Single nephron filtration rate was found to increase in direct proportion to increases in glomerular plasma flow after either plasma or saline loading. However, the dependency of filtration rate on renal plasma flow was not reported in the dog. Significant increases in renal plasma flow in the dog following vasodilation with acetylcholine, prostaglandin or bradykinin have little or no effect on simultaneously measured filtration rate.\textsuperscript{7–9} This independence of filtration rate and renal plasma flow is consistent with filtration pressure disequilibrium.\textsuperscript{17} Filtration pressure disequilibrium is due to higher glomerular capillary pressures and lower filtration coefficients in the dog than in the rat.\textsuperscript{18} Thus, in the dog the increase in renal plasma flow has no effect on filtration. In the present study, the superimposition of acetylcholine to glucagon resulted in a significant decrement of GFR with a significant dilation of efferent arteriole, even though a significant increase in RBF. This result supported the above concept that the changes in RBF had no effect on filtration.

An another factor responsible for the increase in GFR is the change in permeability coefficient of glomerular capillary by glucagon. As shown in Table III, glucagon did not affect the permeability coefficient which was measured within non-autoregulatory range. But, since this measurement was indirect, the further experiment was needed to give a decisive answer.

The last problem is the effects of glucagon on the intrarenal hemodynamics. Horster and Thurau\textsuperscript{11} reported that in low sodium rats the superficial nephron GFR was smaller than the juxtaglomerular nephron GFR. The same result was also obtained in the dog\textsuperscript{19,20} Then the effect of glucagon on an intrarenal distribution of blood flow was examined to assess the redistribution of glomerular filtration. Intrarenal infusion of glucagon at a rate of 0.5 μg/kg.min increased the flow rates in all zones, but the responses to glucagon were not different among zones, suggesting no redistribution of glomerular filtration by glucagon. On the other hand, secretin resulted in a marked redistribution of blood flow from the outer cortex to the inner cortex, i.e., a significant decrease in the percent of total RBF in zone 1 and significant increases in zone 3 and 4.\textsuperscript{21} This effect of secretin was similar to that of other vasodilators, acetylcholine, prostaglandin and bradykinin\textsuperscript{22,23} From the above findings, we concluded that the effect of glucagon on GFR depended on the selective dilation of afferent arteriole, and that as a result of its dilation the net filtration pressure increased without any changes in permeability of glomerular capillary and a distribution of glomerular filtration.

There are many articles about the metabolic effects of glucagon upon the various tissues.\textsuperscript{24–26} Glucagon activates cardiac and hepatic phosphorylase, and cyclic AMP levels in adipose tissue are increased by glucagon. Lucchesi\textsuperscript{25} reported that the cardiac actions of glucagon were mediated through an increase in the intracellular concentration of cyclic AMP. We have previously reported that the intrarenal infusion of dibutylryl cyclic AMP produced the increases in RBF and GFR\textsuperscript{27} indicating a similarity between glucagon and exogenously administered dibutyryl cyclic AMP. Although McKenna et al\textsuperscript{28} reported the rich adrenergic innervation in afferent arterioles, there is no evidence about the distribution of adenyl cyclase in renal arterioles. The hypothetical process in which glucagon activates the adenyl cyclase in the afferent arteriolar wall and dilates selectively the afferent arteriole through the increment of intracellular cyclic AMP, remains to be proven.

Finally, the selective dilation of afferent arterioles was observed with the autoregulatory phenomena, i.e., the pressure reduction within the autoregulatory range resulted in a selective dilation of afferent arterioles\textsuperscript{7,29} and maintained both RBF and GFR. Therefore, it seemed that
glucagon was a suitable tool to clarify the autoregulatory mechanism of RBF and GFR.

REFERENCES


