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The Role of Magnesium on the Renal Blood Flow in Rabbit Kidney

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Introduction

A number of studies have shown that the mammalian kidney has an ability to hold its blood flow constant despite the variations of renal arterial pressure over the physiological and pathological range of 80-200 mmHg[1,2]. The mechanism which produces the unique behavior of the renal vascular bed is not known with certainty.

Several postulations were made in the past. Kinter and Pappenheimer[2] have reported that an increase in renal arterial pressure resulted in an increase in the hematocrit-ratio of intrarenal blood. They postulated that the accompanying increase in viscosity of intrarenal blood was the cause of the autoregulation of renal blood flow.

Other workers[3,4], however, found that the constancy of renal blood flow despite the changes in renal arterial pressure occured in the isolated dog kidney perfused with solution of dextran without red blood cell. Hinshaw and associates[5] have proposed that the renal tissue pressure plays a causal factor in the autoregulation of the renal blood flow. In view of the other findings, Miles[6] have concluded that autoregulation was an active mechanism because cyanide eliminated the autoregulation.

Recently, the myogenic response of the arteriolar muscle was implicated as a possible factor in autoregulation[7,8,9]. So far, several mechanisms have been presented to explain the autoregulation of the renal blood flow, but they are, as yet, not fully conclusive.

The present study has been designed to determine the effect of cations upon the renal vascular bed of rabbit kidney. Solutions of magnesium or calcium chloride in 0.9% saline were perfused into the renal artery under varying levels of perfusion pressure.

Methods

Thirty nine medium-sized rabbits anesthetized with 25% urethane and 3 mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg) were used throughout the experiments. The right kidney, the branching part of the renal artery and the abdominal part of the right ureter were surgically exposed and the renal artery, renal vein and ureter were dissected freely from the surrounding tissues.

An arterial cannula was inserted into the renal artery and was tied around its beaded tip. The kidney was then excised and transferred quickly to a perfusion system and immersed in a thermostatically controlled water bath filled with Locke's solution at 38.5°C. Heparin injected into the vena cava was used as anticoagulant.

The perfusion system was similar to that discribed by Shipley et al[10]. In each of the kidneys of this study the perfusion pressure in the renal artery

was first adjusted to equals the mean systemic arterial pressure (an average of 90 mmHg) and maintained there for approximately 10 minutes, to allow stabilization of kidney function. Then the perfusion pressure was changed to various values. The pressure was increased in 30 mmHg steps up to 370 mmHg, and the renal blood flow and urine flow were measured at each pressure level. After each change of pressure, 1 minute was always allowed for stabilization before collection of blood and urine samples.

The flows at each pressure level were measured by means of a graduated cylinder and a stop-watch.

Results

The absence of autoregulation of renal blood flow in the isolated rabbit kidney:

Seven isolated rabbit kidneys were perfused with Locke's or Tyrode's solution without dextran under various levels of perfusion pressure. These results are represented in Fig. 1, in which is shown that each increase in the renal arterial pressure was always followed by a proportionate increase in the renal blood flow and that in no instance was there any evidence of autoregulation of the renal blood flow.

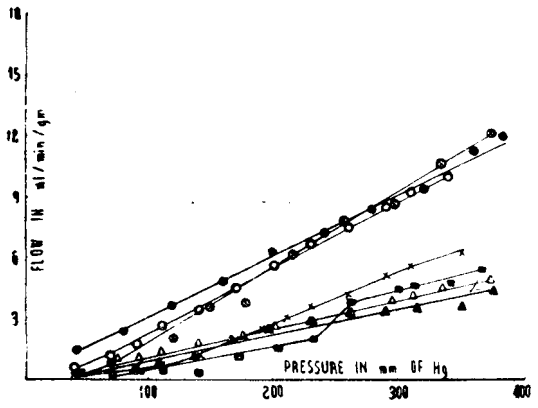

Fig. 1. Absence of autoregulation of flow in 7 rabbit kidneys perfused with Locke's or Tyrode's solution.

In the isolated dog kidney, however, autoregulation of the renal blood flow was present. The curves in Fig. 2, show the results in 3 isolated dog kidneys perfused with Tyrode's solution in the same manner as in the rabbits represented in Fig. 1. These results are in agreement with other report[8].

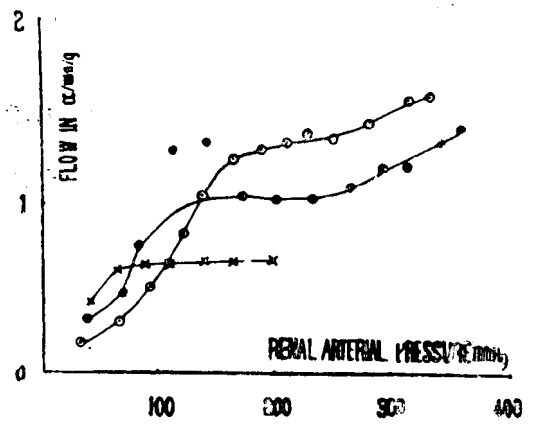

Fig. 2. Autoregulation of flow in 3 dog kidneys perfused with Tyrode's solution without dextran.

The urinary outflow increased with each increase in perfusion pressure both in the rabbit and dog kidneys.

The effect of magnesium ions on the renal blood flow:

Seven rabbit kidneys were perfused with 0.5 mM magnesium chloride in 0.9% sodium chloride solution. The renal flow of the perfusion fluid increased as the perfusion pressure was increased up to the pressure range of 200-370 mmHg. Data are shown in Fig. 3.

In the pressure-flow curves presented in Fig. 3, an inflection was observed in the region of 200-250 mmHg. Below the inflection point the response of flow to pressure was essentially proportional.

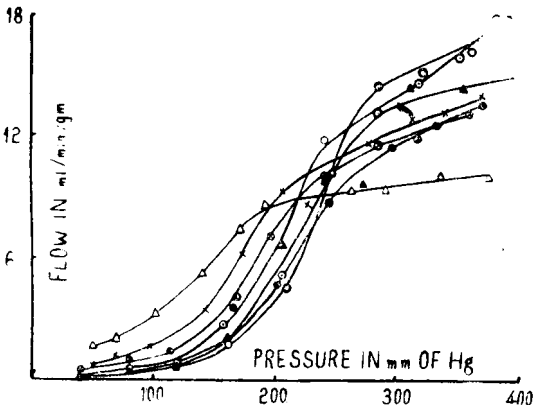

Fig. 3. Effect of varying the renal arterial pressure on blood flow through the rabbit kidneys perfused with 0.5 mM magnesium chloride in 0.9% sodium chloride solution.

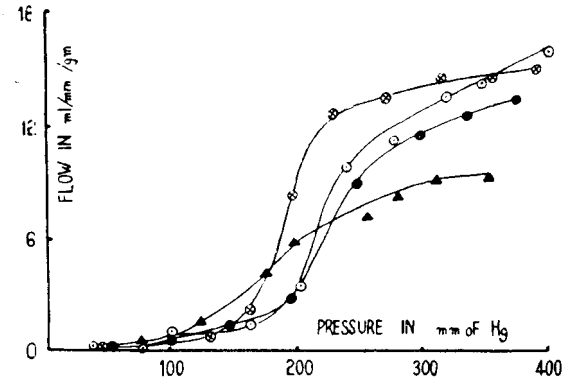

Fig. 4. Effect of varying the renal arterial pressure on blood flow through the rabbit kidneys perfused with 1.0 mM magnesium chloride in 0.9% sodium chloride solution. The curves are typically sigmoid showing the autoregulation.

Above the inflection point the flow was relatively independent from the pressure, showing the development of autoregulation. These results indicate that autoregulation of flow can result from an effect of magnesium ions upon the renal vessels.

After the first pressure-flow study was performed, the perfusion pressure was lowered to a level of 40 mmHg and the pressure-flow study was repeated, increasing the perfusion pressure 30mmHg each time.

In the second determination of the pressure-flow curves, there were almost linear relationships in all cases. Therefore, it appeared that the autoregulation of blood blow in the rabbit kidney perfused with 0.5 mM magnesium chloride in 0.9% sodium chloride could be demonstrated only for the first 30 minutes and disappeared rapidly thereafter.

Further, four isolated rabbit kidneys were perfused with 1.0 mM magnesium chloride in 0.9% sodium chloride solution. The pressure-flow relationships were typical sigmoid curves as shown in Fig. 4, indicating a decreased rate of renal flow elevation in the pressure range of 250–370 mmHg.

Fig. 3 and Fig. 4 show that no significant change in the pressure-flow pattern occurs after slight change of magnesium chloride concentration.

On the other hand, in nine isolated rabbit kidneys which were perfused with 1.5 mM magnesium chloride in isotonic saline, the renal blood flow increased as the arterial pressure was elevated from 40 mmHg to 260 mmHg. In these cases, the perfused kidneys were ruptured at a level of 200-260 mmHg of arterial pressure in every case. It seemed that the active contraction of blood vessels is replaced by dilatation at a level of 100-120 mmHg of arterial pressure, when the magnesium concentration is elevated.

The effect of magnesium and calcium ions combined on the renal blood flow:

Fig. 5 shows the effect of magnesium and calcium ions combined on the pressure-flow pattern of isolated rabbit kidney. In these studies, the kidneys were

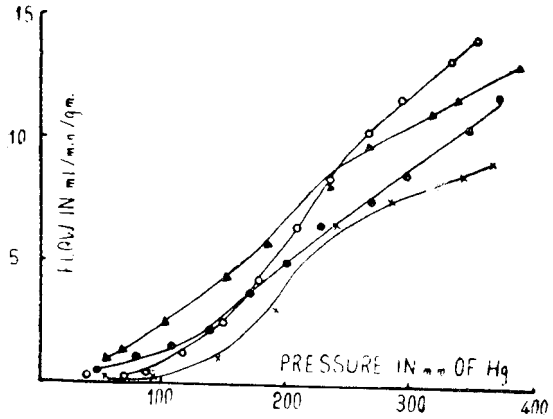

Fig. 5 Effect of varying the renal arterial pressure on blood flow through the rabbit kidneys perfused with magnesium and calcium chloride in 0.9 % sodium chloride solution.

perfused with 0.5 mM magnesium and 1.2 mM calcium chloride in isotonic saline. The renal blood flow increased as perfusion pressure is elevated over the entire range of pressures studied. Thus there was little evidence of autoregulation of the renal flow. This was due apparently to the elimination of the effect of magnesium on the renal vascular beds indicating that calcium and magnesium ions each reciprocally affects upon the smooth muscle of blood vessles[10].

The effect of calcium ions on the renal blood flow:

The perfusate used in this experiment was a solution of 1.2 mM calcium chloride in isotonic saline. The results are shown in Fig. 6. The pressure-flow curves indicate an increased rate of the renal blood flow as the perfusion pressure was elevated

over a range of 250-370 mmHg.

It can be seen that there is a rather consistent increase in flow as the perfusion pussure is increased.

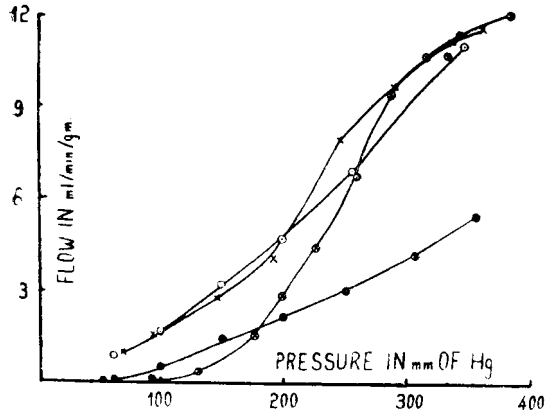

Fig. 6. Pressure-flow relationships in the isolated rabbit kidneys which were perfused with calcium chloride in isotonic saline.

The effect of perfusion of magnesium solution saturated with oxygen:

The flow response of the isolated kidney perfused with 0.5 mM magnesium chloride in isotonic saline solution saturated with oxygen to change in perfusion pressure are shown in Fig. 7. The curves representing the pressure-flow relationships became progressively concave to pressure axis, indicating the development of autoregulation. The typical sigmoid curves show a smaller rate of increase in the renal blood flow as the perfusion pressure is increased over the pressure range of 230-270 mmHg. This pressure-flow response was not significantly different from that obtained by the perfusion of solution with only magnesium chloride.

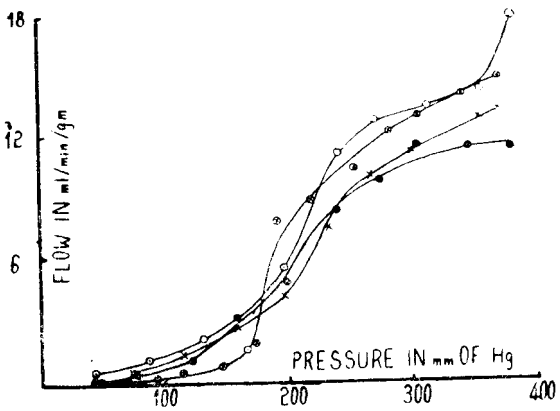

Fig. 7. Pressure-flow relationships in isolated rabbit kidneys perfused with oxygenated magnesium chloride in isotonic saline.

Discussion

It has been generally agreed that the mammalian kidney has a unique ability to autoregulate its blood flow when the renal arterial pressure is varied within physiological range. Kinter and Pappenheimer[2] stated that the hematocrit ratio of the intrarenal blood is a causal factor in the autoregulation of the blood flow. Others have demonstrated the presence of autoregulation of the renal blood flow in the isolated dog[3,4,12] or rat kidneys[3] perfused with dextran solution without red blood cells.

The results of the present study show that the autoregulation is present in the isolated dog kidney perfused with the Locke's solution. In the isolated rabbit kidney, however, autoregulation of the renal blood flow could not be demonstrated when the kidney was perfused with the Locke's solution. Furthermore, the isolated rabbit kidney demonstrated a steady state flow which showed relatively little change over a wide range of the perfusion pressure when the kidney was perfused with normal saline solution containing magnesium ions. Since this presusre-flow response occured even though an increased intrarenal pressure is maintained, it must be resulted from an active contraction of vascular smooth muscle. It seems to indicate that magnesium ions give rise a similar effect as adenosinetriphosphate which shows a contraction of the vascular smooth muscle[14]. This effect of magnesium on the renal blood flow was abolished by addition of calcium into the perfusion fluid. Considering from the fact that magnesium and calcium ions act antagonistically on the smooth muscle of blood vessel[11], results of this study suggest that the autoregulation of the renal flow can be explained on the basis of the myogenic responese of blood vessels.

Bayliss[15] considered that the contraction of vascular smooth muscle was a direct myogenic response to change in wall tension. Others[16,9] have presented the fact that the process of autoregulation seems to indicate the existence of a transient period after each increase in the perfusion pressure during which the blood vessel wall stretches and the flow

increases. This increase in flow, however, diminishes again by constriction of the vessel inspite of the increase in pressure. Therefore, in the interpretation of the present results, it can be assumed that the smooth muscles of the arteries are partially contracted due to the action of magnesium ions and myogenic basal tone, and that a stretch of the muscle caused by elevated pressure in the lumen would bring an increased contractility and thus strengthen the total tension in the wall. Since the caliber of the vessel is determined by the equilibrium between the tension in the wall and the pressure in the lumen, the greater the active tension is induced by stretch the greater decrease in the caliber the of the vessel at the elevated perfusion pressure would ensue. In this way, an increase in perfusion pressure would results in a less increment in blood flow than would be expected otherwise.

In recent reports by Hinshaw and his co-workers[3,5], it was shown that the tissue pressure plays a possible role in autoregulation of renal blood flow and it results from passive change in the caliber of veins due to a rise in tissue pressure. However, Haddy[17] suggested that the increase in resistance at the higher range of flow rate clearly resulted from a rise in resistance to flow in small blood vessels and a fall in the resistance in veins. Therefore, the caliber change occurs in the small vessels rather than in the veins.

Another possibility relating to flow changes may be that autoregulation of blood flow is maintained by a metabolic stimulus. The smooth muscle may be sensitive to the concentration of metabolites in their environment. Guyton and co-workers[18] concluded that the local tissues could autoregulate their blood flow to help maintain an adequate supply of oxygen, and the oxygen lack could cause vasodilation because the vascular muscles would have insufficient oxygen to maintain contraction. On the other hand, Levey[19] showed that the reduction of blood flow was attended by a proportionate diminution in oxygen consumption in the isolated dog kidney.

In the present experiments the blood flow patterns of the kidneys which were perfused with oxygenated magnesium chloride solution and kidneys which were perfused with only magnesium chloride solution without oxygen were not significantly different.

In recent works of Langston and associates[20] they reported that the kidney did not normally autoregulate its blood flow when the kidney was not subjected to surgical trauma. They suggested that the phenomenon of autoregulation of renal blood flow was related to renal damage incident to exposure of the kidney and cannulation of the renal artery. Haddy[21], however, using a technique which kept the kidney intact suggested that the kidney regulated its blood flow in a manmer similar to that observed in kidneys studied by relatively traumatic techniques. If the autoregulation of renal blood flow is induced by surgical trauma, it would occur in the rabbit kidneys perfused with only the Locke's solution to the contrary of what obtained in this experiment.

Recently, it was shown that the phenomenon of autoregulation was due to an active response of smooth muscles of the arteries and arterioles to a change in the intravascular pressure[7,8,9]. It suggested that the blood flow response to a change in the intravascular pressure was a characteristics of the smooth muscles of these vessels. Accordingly the smooth muscle will contract when a tension is applied, as was first suggested by Bayliss[14].

Regardless of the cause of the renal autoregulation, the results of the present experiments show that autoregulation of the renal blood flow was observed in isolated rabbit kidneys perfused with solutions containing magnesium ions, but not in kidneys perfused with solutions containing magnesium and calcium ions which reciprocally affect the smooth muscles of the blood vessels. This suggested that the renal autoregulation is due to the sensitivity of vascular smooth muscle to the change in tension.

Summary

The relationship of pressure to flow was studied in the renal vascular bed of the isolated rabbit kidneys which were perfused with various solutions containing cations under various levels of perfusion pressure. Magnesium and calcium ions in normal saline solution were perfused into the renal artery.

Three isolated dog and 39 rabbit kidneys were used. The following results were obtained.

1) There was autoregulation of flow in the isolated dog kidneys perfused with Tyrode's solution without dextran.

2) There was no autoregulation of renal blood flow in the isolated rabbit kidneys perfused with Tyrode's or Locke's solution without dextran.

3) The renal blood flow was autoregulated in the isolated rabbit kidneys when the magnesium chloride in isotonic saline was perfused. It was discussed that magnesium ions affected the contractility of the renal vascular smooth muscle.

4) The autoregulation of flow which was induced by perfusion of magnesium ions was abolished by addition of calcium ions. Magnesium and calcium ions seemed to have an antagonistic effects upon the smooth muscles of the renal vascular bed.

5) In the pressure-flow relationship, a change in perfusion pressure always resulted in a corresponding change in the renal blood flow when the isolated rabbit kidneys were perfused with calcium chloride in isotonic saline solution.

6) The pressure-flow pattern was not significantly different from each other when magnesium-added fluid was given with or without oxygenation.

7) It is concluded that autoregulation of the renal blood flow is attributable to the sensitivity of vascular smooth muscles to the change in tension of the wall of the blood vessel.

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국 문 초 록

토끼 콩팥의 혈액 유통에 대한 막네슘의 구실

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적출한 토끼 콩팥의 동맥에 각기 다른 용액을 관류하면서 압력 변동에 따르는 압력과 유통량의 관계를 실험하였다. $MgCl_2$와 $CaCl_2$ 용액을 각기 콩팥 동맥에 관류하여 토끼 콩팥 혈액유통에 대한 이들 이온의 영양을 보았다. 3마리의 개와 39마리의 토끼의 콩팥을 사용하여 다음과 같은 성적을 얻었다.

1. Tyrode씨 용액으로 적출한 개의 콩팥을 관류하면 자동조절이 나타났다. 개의 콩팥의 자동조절은 dextran의 영양을 받지 않음을 지적할 수 있다.

2. 적출한 토끼 콩팥을 Tyrode씨 용액으로 관류하면 자동조절이 일어나지 않았다.

3. 생리식염수에 $MgCl_2$를 첨가한 용액으로 토끼 콩팥을 관류하면 자동조절이 나타났다. 이는 막네슘 이온이 콩팥 혈관벽 평활근의 수축에 영향을 미쳐서 일어나는 현상이라고 생각된다.

4. 생리식염수에 $MgCl_2$와 $CaCl_2$를 같이 첨가하여 적출한 토끼 콩팥을 관류하면 자동조절이 나타나지 않았다. 이는 막네슘 이온과 칼슘 이온의 혈관벽 평활근에 대한 길항작용에 기인하는 것이라고 생각한다.

5. 생리식염수에 $CaCl_2$를 첨가하여 적출한 토끼 콩팥을 관류하면 압력의 변화에 따라서 유통량이 증가하였다.

6. $MgCl_2$ 용액으로 적출한 토끼 콩팥을 관류할 때와 이 관류액을 산소로 포화시켜서 관류할 때는 압력과 유통량 관계는 별다른 차이를 나타내지 않았다.

7. 콩팥의 혈액 유통의 자동조절은 장력에 대한 혈관 평활근의 감수성에 기인할 것임을 고찰하였다.

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