

On the action of adrenalin and pituitrin upon the glomerular capillaries and on their diuretic action.

By

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Introduction.

Since the time of Bowman and Ludwig it has been recognized that alterations in the renal circulation play an important part in the adjustment of renal function to urinformation.

At present it is believed that the mechanism of urinformation is performed by the following two processes.

1. Filtration process in the glomeruli.
2. Reabsorption process in the tubules.

The filtration process in the glomeruli is proportional to the blood pressure in the glomerular capillaries and also to the quantity of blood which flows through the glomerular capillaries.

Richards and Plant reported that minute doses of adrenalin and pituitrin, in the perfusion experiments, caused diuresis, the rise of renal blood pressure and the increase in kidney volume.

They regarded the diuresis and kidney swelling due to increased glomerular pressure resulting from constriction of the vas efferents. But they added that the changes in the afferent and efferent vessels are so beyond their control or powers of observation that it is impossible to devise at the present time any crucial experiment which might decide the nature of the process occurring in the glomeruli.

In the perfusion experiment of kidney, however, it can not be decided whether the action of these substances is upon the renal arteries or upon the glomerular capillaries.

I made the following experiments to measure changes in the calibre of glomerular capillaries and to examine increase and decrease of the number of glomeruli, each solution of these drugs being directly applied to the exposed kidney of frog under observation with the microscope.

Method.

In the majority of experiments *Rana nigromaculata* was used; in some, *Rana esculenta*. The brain was destroyed by pithing or the animal was narcotized slightly with curara.

The kidney was exposed by longitudinal abdominal incision.

For intravenous injection, a glass canula was tied in to its central stump. The abdominal cavity was held open by pins thrust through the right parietal wall. In female frogs the ovaries and sometimes the right oviduct were dissected out, hemorrhage being prevented by ligature. In male frogs, in experiments in which observations of a large surface of the kidney were desired, the right testis and fat bodies were excised after ligature of their vessels.

Illumination of the kidney was best secured by means of an arc-lamp. The rays were condensed by the proper lens and were cooled by passage through a layer of water tinged with methylene blue contained in a rectangular museum jar of 50 mm. thickness.

The light was directed at the ventral surface of the kidney at an angle of 30—40 degrees. It was important that the ventral surface of the kidney should lie as nearly as possible in a horizontal plane.

Surface reflections and drying were prevented by laying a small fragment of cover slip on the ventral surface.

The area of the kidney surface found to be most suitable for study is the space between the adrenal body and the outer border.

State of glomeruli.

Flow of blood in the glomeruli is rapid or slow, constant or intermittent, depending on the condition of the animal and amount of blood lost during the preliminary operation. The arterial circulation can be distinguished by the direction of its flow and its greater rapidity.

In the interstices of the veins one sees circular arrangements of capillaries which are obviously glomeruli.

Movement of blood in them varies: in some it is of bewildering rapidity through a maze of pathways: in others, it is a slower progression of cells through fewer channels.

The number of active glomeruli to be found on inspection of the ventral surface of the kidney varied greatly indifferent animals, and also in the same animal under different conditions.

In on animal, a single field may show as many as ten; in another, only two or three are to be found on searching the entire available surface of the kidney. The number of glomeruli through which blood circulates visibly at any moment is not necessarily the total number of glomeruli in the kidney.

The number of capillaries in a single glomerulus through which blood visibly flows is not necessarily the total number of capillaries in the tuft. In many preparations I have

observed that the flow of blood through the glomerular capillaries may show occasional interruptions.

They are not synchronous with diastole of the heart; they are not regular in occurrence, and they do not involve all the glomeruli under observation in a single field to the same degree.

In some instances blood flow stops and the corpuscles disappear from the capillaries: in others, on cessation of blood flow, the corpuscles remain motionless in the capillaries throughout the interruption. Changes in glomerular capillary calibre may be induced by changes in extra and intra capillary pressure. Extra capillary pressure would appear to be a more important influence in relation to capillaries of the glomerular tuft than in capillaries elsewhere because of the existence of the highly elastic Bowman's capsule in which they are inclosed. Changes in glomerular capillary calibre can also be induced by the changes in intra capillary blood pressure which may result from changes in arterial pressure, in the calibre of afferent or efferent vessels.

Experiments.

1. Adrenalin.

The diuretic action of small doses of adrenalin has been noted by Barbier and Frenkel, by Houghton and Merrill and by Biberfeld. Houghton and Merrill obtained their result by intravenous injection of 0.01 mgm. into dogs; Biberfeld by 2 mgm. subcutaneously in rabbits. Both Barbier and Frenkel and Jost interpret the oncometric record to mean dilatation of renal vessels.

This explanation of the diuretic action of adrenalin is commonly accepted. Richards and Plant, as I have mentioned, reported that minute doses of adrenalin, in the perfusion experiments, caused rise of renal blood pressure, diuresis and increase in kidney volume.

In my experiments a drop of adrenalin, in various concentrations was placed on the glomeruli under observation with the microscope, by means of a fine glass capillary which has been made as fine as possible.

When a drop of adrenalin in dilution 1 : 100,000 was applied to the glomeruli the vas afferents always contracted completely and accordingly the blood flow in the glomerular capillaries disappeared and a number of glomeruli observed became invisible.

When adrenalin in dilution between 1 : 1,000,000 and 1 : 5,000,000 was applied to the glomeruli in drops, the glomerular capillaries were dilated and the circulation in them became much more rapid.

The glomeruli which had hitherto been stationary, became active and got congested and swollen. A number of glomeruli unobserved until then became visible.

The following table shows the results produced by application of adrenalin in various dilution.

| Case. | Dilution. | Variation of diameter of glomerular capillaries. | Variation of the number of glomeruli | | Variation of the state of circulation in the glomeruli. |
|-------|---------------|--------------------------------------------------|--------------------------------------|-----------------|---------------------------------------------------------|
| | | | Before applicat. | After applicat. | |
| 1 | 1 : 100,000 | } contracted. | 8 | 2 | } became more slow or stopped. |
| 2 | " " | | 7 | 5 | |
| 3 | " " | | 10 | 3 | |
| 4 | " " | | 4 | 0 | |
| 5 | " " | | 5 | 1 | |
| 6 | 1 : 1,000,000 | } dilated. | 6 | 9 | } became more rapid. |
| 7 | " " | | 3 | 8 | |
| 8 | " " | | 6 | 10 | |
| 9 | " " | | 4 | 7 | |
| 10 | " " | | 6 | 8 | |
| 11 | 1 : 2,000,000 | } dilated. | 3 | 6 | } became more rapid. |
| 12 | " " | | 5 | 7 | |
| 13 | " " | | 4 | 7 | |
| 14 | " " | | 4 | 8 | |
| 15 | " " | | 3 | 6 | |
| 16 | 1 : 5,000,000 | } dilated remarkably. | 5 | 8 | } became much more rapid. |
| 17 | " " | | 3 | 5 | |
| 18 | " " | | 2 | 7 | |
| 19 | " " | | 6 | 10 | |
| 20 | " " | | 7 | 11 | |

But when adrenalin in dilution 1 : 1,000,000—2,000,000 was injected into the anterior abdominal vein in amounts ranging from 0.05 to 0.1 cc., the glomerular capillaries would be contracted and the glomeruli, hitherto observed, became invisible.

It is to be presumed that these results are owing to the contraction of renal arteries.

On the other hand, a more diluted solution than 1 : 5,000,000, when it was injected, caused dilatation of glomerular capillaries and the glomeruli were congested and swollen and the circulation of glomerular capillaries through which the blood flows became more rapid. As the control 0.1 cc. of 0.65 p. c. Ringer's solution was injected but it showed no visible change.

2. Pituitrin.

Magous and Schäfer and Schäfer and Herring were the first to recognize and investigate the diuretic action of extracts of the pituitary body.

They explained the diuresis as due to direct stimulation of the renal epithelium. Their conclusion was based on the lack of parallel between the diuretic effect on the one hand and the blood pressure and kidney volume on the other hand.

Hoskins and Means have supported Schäfer's view.

An opposite conclusion has been arrived at by Houghton and Merill and by King and Stoland. From a comparison of the blood pressure, kidney volume and urin flow they considered that the vascular changes following the injection of pituitary extract are sufficient to explain the diuresis. Pale and Cow working with isolated arterial rings, after the method of Meyer, found a specific dilator action on the renal vessels. McCord found that the vessels of the isolated perfused kidney were dilated by pituitary extract while the vessels of other organs were constricted. Richards and Plant held that in the perfusion experiments, minute doses of pituitrin caused diuresis and it was due to increased glomerular pressure resulting from constriction of the vas efferents.

But perfusion of any isolated organ is less satisfactory than when it was performed in Situ of that organ.

In my experiments a drop of pituitrin, in various dilution, was applied to the exposed kidney surface. Commercial preparation of Park, Davis Co. was used.

When a drop of pituitrin was applied to the glomeruli by means of a fine glass capillary which has been made as fine as possible, observing with microscope, the afferent vessels contracted and accordingly the glomerular circulation disappeared and also the number of visible glomeruli decreased.

A solution 1 : 2—1 : 20 in dilution when it was placed on the surface in drops, caused dilatation of afferent vessels and glomerular capillaries, and accordingly the glomerular circulation became so rapid that the corpuscles could not be distinguished and the glomeruli themselves got congested and swollen.

A number of glomeruli, hitherto unobserved, became visible, for instance, the number of glomeruli, 3 or 4 before application increased to the number of 10—12 after application.

The following table shows the results of my experiments.
(direct application)

| Case. | Dilution. | Variation of the number of glomeruli. | | Variation of diameter of glomerular capillaries. | Variation of the state of circulation in the glomeruli. |
|-------|-----------|---------------------------------------|-----------------|--------------------------------------------------|---------------------------------------------------------|
| | | Before applicat. | After applicat. | | |
| 1 | 1 : 0 | 7 | 5 | contracted slightly. | became more slow. |
| 2 | ∅ | 5 | 3 | contracted. | ∅ |
| 3 | ∅ | 8 | 6 | ∅ | ∅ |
| 4 | ∅ | 3 | 3 | contracted slightly. | no change. |
| 5 | ∅ | 7 | 6 | ∅ | became more slow. |
| 6 | 1 : 2 | 5 | 8 | dilated. | became more rapid. |
| 7 | ∅ | 9 | 12 | dilated remarkably. | ∅ |
| 8 | ∅ | 7 | 11 | ∅ | became much more rapid. |
| 9 | ∅ | 4 | 7 | dilated. | ∅ |
| 10 | ∅ | 6 | 7 | dilated slightly. | became more rapid. |
| 11 | 1 : 4 | 8 | 11 | dilated. | ∅ |

| | | | | | |
|----|------|----|----|---------------------|-------------------------|
| 12 | 1:4 | 3 | 6 | dilated. | became more rapid. |
| 13 | ◇ | 5 | 5 | dilated slightly. | no change. |
| 14 | ◇ | 4 | 6 | dilated. | became more rapid. |
| 15 | ◇ | 5 | 9 | dilated remarkably. | became much more rapid. |
| 16 | 1:8 | 6 | 7 | ◇ | ◇ |
| 17 | ◇ | 4 | 7 | dilated. | ◇ |
| 18 | ◇ | 7 | 10 | dilated remarkably. | ◇ |
| 19 | ◇ | 6 | 7 | dilated slightly. | became more rapid. |
| 20 | ◇ | 3 | 5 | dilated. | ◇ |
| 21 | 1:10 | 10 | 10 | no change. | no change. |
| 22 | ◇ | 3 | 5 | dilated. | became more rapid. |
| 23 | ◇ | 4 | 6 | ◇ | ◇ |
| 24 | ◇ | 6 | 8 | ◇ | ◇ |
| 25 | ◇ | 7 | 10 | ◇ | ◇ |
| 26 | 1:20 | 5 | 6 | dilated slightly. | ◇ |
| 27 | ◇ | 4 | 4 | no change. | no change. |
| 28 | ◇ | 3 | 5 | dilated. | became more rapid. |
| 29 | ◇ | 8 | 10 | ◇ | ◇ |
| 30 | ◇ | 7 | 7 | dilated slightly. | ◇ |

When the pituitrin in dilution 1:2—1:10 was injected into the anterior abdominal vein in amounts of 0.05—0.1 cc., the glomerular capillaries were contracted and glomeruli, hitherto active, became inactive and disappeared.

The solution 1:20—1:30 in dilution, when it was injected, showed dilator effect upon the glomerular capillaries and glomeruli got congested and swollen.

Glomerular circulation became more rapid and the number of glomeruli increased.

Conclusion.

Direct application of adrenalin and pituitrin in minute amounts of doses to the exposed renal surface, causes dilatation of glomerular capillaries and the great rapidity of the blood circulation in the glomeruli. The quantity of blood flowing through the glomeruli, increases and accordingly the glomeruli are congested and swollen. But in larger doses adrenalin and pituitrin cause contraction of afferent and efferent vessels and also of glomerular capillaries.

A number of glomeruli, hitherto observed, becomes invisible.

In my experiments I could not find that the efferent vessels only were especially contracted.

Diuretic action of minute doses of adrenalin and pituitrin, though it has been persisted to be due to contraction only of efferent vessels by Richards and Plant and many others in perfusion experiments, seems to be due not only to contraction of efferent

vessels but to dilatation of glomerular capillaries and to the increase of the quantity of blood which flows through the glomeruli and increase of the number of active glomeruli.

In conclusion, allow me to give my hearty thanks for my indebtedness to Prof. S. Oinuma.

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内容大意

「アドレナリン」及ビ「ピツイトリン」ノ腎臓糸絨體毛細血管ニ 及ボス作用竝ニ其利尿作用ニ就テ

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Bowmann 竝ニ Ludwig 以來腎臓ニ於ケル血液循環ノ變化ハ腎臓ノ尿生成機轉ニ重要ナル意義ヲ有スル事ガ一般ニ承認サレ現今ニテハ尿生成機轉ハ次ノ二作用ニヨリテ營マルト信ゼラル即チ糸絨體ニ於ケル濾過作用及ビ細尿管ニ於ケル再吸收作用ナリ。而シテ糸絨體ノ濾過作用ハ糸絨體毛細管内ノ血壓竝ニ其毛細管ヲ通ジテ流ル血液ノ量ニ比例ス。

少量ノ Adrenalin 及ビ Pituitrin ハ腎血壓ノ上昇竝ニ腎容積ノ増加ヲ來タス事ハ Richards 竝ニ Plant 及ビ其他ノ人々ニヨリテ報告サレ而シテ之等ノ結果ノ唯一ノ原因トシテ輸出血管ノ收縮ヲ擧ゲタリサレド之等ノ成績ハ皆テ灌流試験ニヨル結果ニシテ灌流試験ハ intakt ノ状態ニ於ケルヨリ不完全ニシテ又之等ノ藥品ガ腎動脈ニ作用スルモノナルヤ又糸絨體毛細血管ニ作用スルモノナルヤヲ觀察スルヲ得ズ故ニ予ハ顯微鏡下ニ糸絨體ヲ觀察シツツ之等ノ藥品ヲ用ヒ（滴下或ハ注射ノ方法ニテ）糸絨體ノ變化、糸絨體毛細管、輸出入兩血管、ノ變化ヲ觀察シタリ。極少量ノ Adrenalin 及ビ Pituitrin ハ共ニ糸絨體毛細血管ノ擴大ヲ來タシ糸絨體ヲ流ルル血流ハ早クナリ糸絨體ハ充血シ且其數ヲ増加ス之ニ反シ少シク多量ヲ用フル時ハ輸出入兩血管、糸絨體毛細管ハ共ニ收縮シ今迄盛ニ活動セル糸絨體ハ活動ヲ止メ其數ヲ減少ス。而シテ之等ノ際輸出血管ノミガ特ニ著シク收縮スルガ如キ例ハ未ダ觀察シ得ザリキ。故ニ少量ノ Adrenalin 及ビ Pituitrin ノ利尿作用ハ輸出血管ノ收縮ノミニ關セズシテ糸絨體毛細管ノ擴大ノ結果糸絨體ヲ流ルル速度竝ニ血量ノ増加及ビ活動セル糸絨體ノ數ノ増加ニ歸スベキモノト推斷セラル。

