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URINARY KALLIKREIN: MECHANISMS OF ITS RELEASE AND ACTION. (REVIEW AND HYPOTHESIS)

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ABSTRACT

Urinary kallikrein is originated in the kidney. In this review it is postulated that urinary kallikrein excretion is related with the necessity to eliminate water. The principal releasing mechanism is a wash-out effect on renal kallikrein, produced by the flow reaching the tabular distal cell. Several systems can modify kallikrein excretion acting on the mechanisms of its release and/or synthesis. Urinary kallikrein regulates extracellular space inhibiting water distal reabsorption.

INTRODUCTION

Four types of kallikrein have been isolated from urine and rat kidney with similar molecular weight, optimum pH and ability to liberate bradykinin from kininogen (36, 37). These characteristics permit to accept that urinary kallikrein is originated in the kidney. Renal kallikrein is located and released into the tubular fluid at the level of the distal nephron tubule (38) and is implicated in the control of water excretion (33).

The purpose of this mini review is to intent, at the light of different studies from our and others laboratories, a theory about the mechanisms regulating renal kallikrein excretion and its possible action in the regula tion of water excretion.

Urinary kallikrein is positively correlated with urine flow in rats (4, 5, 23, 26, 28), rabbits (33) and humans (34). This implicates that both parameters are related. An increase in urine flow rate has been reported to be associated with a concomitant increase in urinary kallikrein excretion (19, 30, 33).

This fact suggests that urinary kallikrein excretion could be dependent of the amount of water that is eliminated. The existence of positive correlation between urinary kallikrein excretion and glomerular filtration rate (GFR) (27) contributes to affirm the previous hypothesis. Rats under osmotic diuresis increase kallikrein excretion and a positive correlation with urine flow but no with GFR (which does not change) s obtained (27). The principal action site of osmotic diuretics within the nephron is at the proximal tubule. Thus, the amount of water that reachs the distal tabular cell is increased and suggesting that this augmented water flow at the distal nephron exerts a wash-out effect on kallikrein excretion (27) under this circunstances.

Urea is filtered, and reabsorbed along the nephron; this reabsorption decreases when urine flow increases (39). A positive correlation between urea excretion and urinary flow and a negative correlation with urinary osmolality has been observed (28). These results suggest that urea excretion is flow-dependent.

Similar correlations were observed when flow and urinary osmolality were correlated to kallikrein excretion instead of urea excretion (26, 28).

Urinary kallikrein and urea excretions were positively correlated too, and the slopes of the regression lines obtained when urea and kallikrein excretions were compared with urine flow and urinary osmolality were similar (28). All these data taken together suggest that urinary kallikrein excretion is flowdependent.

Urine flow is directly associated with the necessity of eliminate water, then is should be related with total body water content. Marin Grez and Carretero (23) reported that kallikrein excretion was related to extracellular fluid volume (ECFV). On the other hand, we observed positive correlations between urinary kallikrein excretion and inulin space, plasma volume and interstitial space without correlation with intracellular water and total body water (24). The positive correlations between urinary kallikrein excretion and ECFV and its components, indicate that these parameters are not independent. Three possibilities could explain this relationship: a) renal kallikrein regulates ECFV, b) ECFV is responsible for urinary kallikrein excretion, c) both parameters are related with a third system not yet known. It is difficult to confirm or to discard the latter possibility at the present time, since there is no data available to date. Accepting that kallikrein increases water excretion (33), the correlation of kallikrein excretion with ECFV should be negative, which is opposite to the observed results, then it is possible to suggest that ECFV regulates kallikrein excretion instead. However, when ECFV components area acutely altered, their correlations with urinary kallikrein excretion disappear (25). Then, it is possible to conclude that the regulatory effect of extracellular space components on urinary kallikrein excretion have not the same degree of importance when water distribution is altered, in acute situations.

Different systems can modify the mechanisms of release or synthesis of renal kallikrein. The relationship between the sympathetic nervous system and renal kallikrein is unclear to date. It has been reported that renal nerve stimulation decreases the kininogenase activity of urine (2). In contrast, it was observed that infusion into the renal artery of subpressor doses of dopamine or noradrenaline increased urinary kallikrein excretion (31, 32). Diz et al. (10) did not observe changes in urinary kallikrein excretion in rats chronically infused with noradrenaline. Vasopressin increased urinary kallikrein excretion in dogs and rats under water diuresis (11, 12). These results were confirmed by Tomita et al. (43) and they also observed that vasopressin was uneffective during normal hydration. Arginine vasopressin significantly increased enzyme release from rat kidney slices (18). We have observed that noradrenaline and vasopressin increased the effect of dextrose hypertonic infusion on urinary kallikrein excretion in acute infused animals without alterations in urinary flow and GFR (4, 29). This suggests that both drugs have a direct action on the mechanism of kallikrein excretion since the renal parameters studied are unaltered. Chronic noradrenaline infusion does not alter kallikrein excretion and chronic vasopressin administration decreases it (29). The effect of dextrose infusión in rats chronically infused with noradrenaline or vasopressin was higher than that obtained in intact animals (29).

These results also showed that in acute experiments noradrenaline and vasopressin increased kallikrein excretion in animals under osmotic diuresis but when both drugs are administered chronically to normal hydrated animals this response was not observed. In the latter group of animals dextrose infusion increased urinary kallikrein excretion (29). These data make possible to assume that both drugs stimulate urinary kallikrein excretion, from the tubular distal cells, only when it is necessary to eliminate an excess of water. If the data of the control groups and those obtained on the different days of the noradrenaline and vasopressin chronically infused rats are pooled, a positive correlation between urinary kallikrein excretion and urine flow is obtained, even though the groups are different (29). This correlation may mean that urinary kallikrein excretion is not dependent on the noradrenaline or vasopressin plasmatic levels in normal hydrated animals.

A great deal of evidence strongly suggests a close and significant relationship between the renal kallikrein and renin-angiotensin systems (45). Angiotesin II did not modified urinary kallikrein excretion, GFR and urine volume in dextrose infused rats (4). This agrees with previous unpublished studies, in the same experimental model, in which the inhibitor of the converting enzyme, SQ 14,225 , did not altered urinary kallikrein excretion, and SQ 14,225 does increase plasma renin activity and decreases angiotensin II formation.

We have observed that the chronic administration of SQ 14,225, SQ 20,881 and saralasin to normal hydrated rats increased kallikrein excretion (5). This effect could be due to the increased urinary flow observed and not to the inhibition of the renin-angiotensin system. Other explanation could be that the increased kallikrein excretion had a relationship with the decreased activity of the renin-angiotensin system since kallikrein excretion increases in those hypertensions characterized by increased steroid level (20, 21). The excessive secretion of mineralocorticoids decreases the renin levels in blood and kidney (1, 3, 14, 15, 17, 40, 46). The similar results obtained with the inhibitors of angiotensin I - converting enzyme and with the competitive inhibitor of angiotensin II suggest that the modifications observed are not due to the inhibition of kininase II (converting enzyme).

Mineralocorticoids are important regulators of kallikrein urinary excretion (13, 22, 35). Kaizu and Margolius (16) observed that isolated rat renal cortical cells produce more kallikrein in response to aldosterone and less in response to spironolactone. This contrasts with other studies showing no significant effect of aldosterone on kallikrein release into urine or into venous effluent of the isolated rat kidney (44). Croxatto and Rosas (7) also observed that aldosterone did not altered urinary kallikrein excretion, in the intact rat, during the ten hours following the first injection, but subsequent administrations of the drug produced a significative increment in kallikrein excretion.

We have observed that aldosterone added to a dextrose infusion increases urinary Kallikrein excretion (4).

Atrial natriuretic factor (ANF) causes an immediate natriuresis and diuresis when is injected intravenous into rats (8, 9, 41). This effect was accompanied by and increased kallikrein excretion (42). This result was confirmed in our laboratory (unpublished results). The abscense, in our experiments, of a correlation between ANF administration and kallikrein excretion could indicate that this response is rather due to the increased water excretion on renal kallikrein excretion.

It has been postulated that renal kallikrein is implicated in the control of water excretion by the kidney. Mills and Ward (33) suggested that kallikrein has an opposite action to vasopressin. We have observed a negative correlation between kallikrein excretion and the reabsorption of water free of solutes (T_cH_2O) (unpublished results). This result could indicate that the distal reabsorption of water is in part inhibited by kallikrein.

These results raise the possibility that renal kallikrein release is related to the necessity to eliminate water, and the principal mechanism of renal kallikrein release could be a wash-out effect produce by the water flow reaching the distal tubular cells. Several humoral systems can modify urinary kallikrein excretion, acting on the mechanisms of its release and/or synthesis. Urinary kallikrein regulates extracellular fluid space by inhibiting water reabsorption at the distal nephron.

RESUMEN

Calicreina Urinaria: Mecanismo de liberación y acción. (Revisión o hipótesis). *Martinez Seeber A., (Fisiología Humana, Departamento de Ciencias Biológicas. Facultad de Farmacia y Bioquímica, U.B.A., JUNIN 956, Buenos Aires, Argentina).* **Invest Clín** *27(3): 213-222, 1986.*– La calicreína urinaria se origina en el riñón. En esta revisión se postula que la

excreción urinaria de calicreína está relacionada con la necesidad de eliminar agua. El principal mecanismo de su liberación es un "lavado" de la calicreína renal producido por el flujo que llega a la célula tabular distal. Diversos sistemas pueden modificar la excreción de calicreína actuando sobre los mecanismos de liberación y/o síntesis. La calicreína urinaria regula el espacio extracelular inhibiendo la reabsorción distal de agua.

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