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Commentary

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Potassium homoeostasis in the elderly

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Introduction

The mechanisms which are involved in potassium homeostasis maintain the serum level within the relatively narrow normal range of 3.5–5.0 mEq/l despite widely varying dietary intake and relatively huge intracellular potassium stores (98% of total body potassium). Abnormalities in renal excretion and/or interference with the physiological control of intracellular to extracellular potassium gradient may upset this fine balance, resulting in abnormalities in serum potassium.[1,2] A complex interaction of renal and extrarenal mechanisms are involved in maintaining this balance. Physiological changes associated with increasing age would tend to predispose the elderly to hyperkalaemia. However, potassium homeostasis in the elderly has not been well studied to date.

In this commentary, renal and extrarenal potassium homeostasis are summarized. Age-related alterations in these mechanisms are highlighted, and the possible clinical implications of such changes are discussed.

Renal mechanisms

The renal tubules can normally adapt to wide fluctuations in potassium intake. The renal excretory capacity for potassium is not exceeded by a dietary intake of 6 mEq/kg/day.[3] The distal convoluted tubule and collecting ducts constitute the sites which control renal potassium excretion (Figure 1). Dietary potassium loading results in both direct[4] and indirect (via increased aldosterone secretion[3]) stimulation of Na^+-K^+ ATPase. This results in a prolonged increase in potassium excretion by enhancing potassium secretion.

Increased renal delivery of sodium[5] and water[6] to the distal tubule may enhance renal potassium excretion, e.g. following loop diuretics,[7] but the physiological importance of this is uncertain. Conversely, decreased delivery of sodium chloride to the distal tubule during periods of avid sodium retention hinders potassium secretion, e.g. prerenal azotemia or severe congestive heart failure.[8] Arginine vasopressin secretion also significantly influences potassium excretion.[9]

Systemic acidosis and alkalosis exert a powerful impact on renal potassium balance.[10] During periods of systemic acidosis, hydrogen ion is buffered intracellularly, with a resultant shift of potassium from the intracellular to the extracellular fluid to maintain electrical neutrality. Thus, the potassium concentration within the distal tubular cells falls, as does the concentration gradient towards the tubular lumen, which culminates in a reduction in potassium secretion. Conversely, a shift of potassium into distal renal tubular cells in systemic alkalosis enhances renal tubular secretion, which contributes to an increase in potassium excretion. The above effects are however modified by the duration of disturbance of acid-base balance, e.g. prolonged acidosis alters fluid delivery, and this complicates the above picture.

The late distal convoluted tubule and cortical collecting duct contain intercalated and principal cells which serve distinct transport functions.[11] The α and β subtypes of intercalated cells secrete hydrogen and bicarbonate ions into the lumen, respect-

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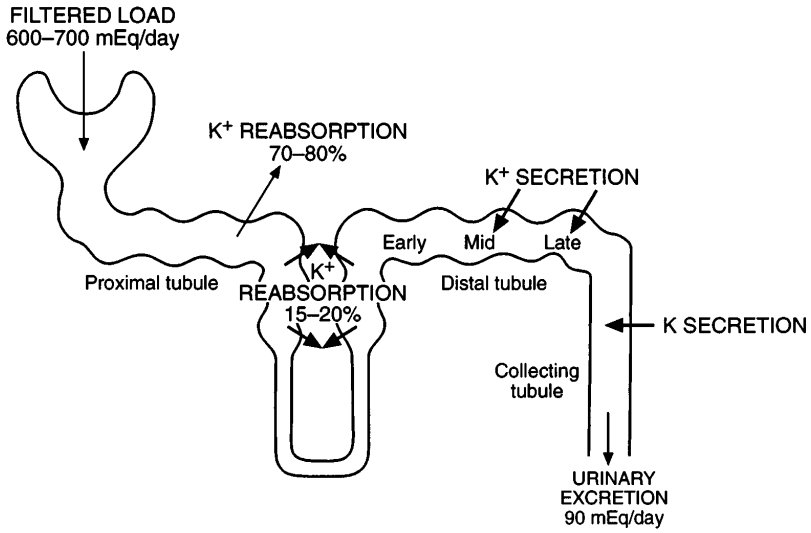

Figure 1. Schematic representation of the renal tubular handling of potassium. About 90% of the filtered potassium is reabsorbed by the early to mid distal tubule. Most of the potassium in the urine is derived from secretion of potassium by the mid to late distal tubule and cortical collecting tubule.

ively. Secretion of hydrogen ions via the H^+-K^+ ATPase leads to reabsorption of potassium, whereas secretion of bicarbonate may influence secretion of potassium.[12] The principal cells are the most numerous, and are the ones responsible for net secretion of potassium. Two complex processes are involved in the secretion of potassium. Firstly, the electrogenic reabsorption of sodium generates a lumen negative transepithelial potential difference. Secondly, there is movement of potassium via specific transport pathways in the apical membrane of principal cells.

Aldosterone is a primary mineralocorticoid, and its secretion is stimulated directly by increased plasma potassium concentration[13] and indirectly by angiotensin II[14] and by ACTH. The actions of aldosterone occur in serial steps which can be divided into early and late phases.[15,16] In the early phase, mineralocorticoids activate the apical sodium conductive pathway and thereby the entry of sodium into principal cells. An increase in sodium within the cytosol increases ion flux via the basolateral Na^+-K^+ ATPase. Continued exposure to mineralocorticoids will result in the late phase changes with the insertion of additional Na^+-K^+ ATPase pump units, and an increase in conductance and density of apical potassium channels.[17]

Aldosterone secretion is closely linked to the renin-angiotensin system, since the sensitivity of the adrenal cortex for aldosterone secretion in response to hyperkalaemia depends on angiotensin II. Renin is secreted in response to salt and water depletion and/or hypoperfusion of the juxtaglomerular apparatus. This stimulation is partially mediated by beta sympathetic agonists[18] and prostaglandins.[19] Atrial natriuretic factor (ANF) is a powerful suppressor of aldosterone secretion.

Extrarenal mechanisms

The extrarenal movement of potassium from the extracellular to the intracellular compartment is also important in the maintenance of normal serum levels. Shifts in potassium can occur in acid-base disorders, especially in metabolic disorders.[20]

Insulin augments cellular potassium uptake by stimulating Na^+-K^+ ATPase associated with increased cellular glucose uptake.[21,22] The stimulating effect of hyperkalaemia on insulin secretion appears to be small.[23]

Aldosterone seems to have relatively minor effects on potassium secretion from the gastrointestinal (GI) tract. However, the potential role of the GI tract in potassium homeostasis needs to be emphasized. Accumulating evidence suggests that the GI tract plays a vital role in controlling potassium balance in severe renal impairment.[24] It is intriguing to speculate upon its potential relevance in the elderly.

Sympathetic adrenergic activity plays an important role in potassium distribution. Beta adrenergic stimulation enhances, and blockade impairs, extrarenal disposal of a potassium load, in the absence of any change in plasma insulin or aldosterone levels or in renal potassium excretion.[25] This increased cellular uptake of potassium is apparently Beta-2-receptor-specific,[26] with the cellular mechanism involving stimulation of cyclic AMP followed by activation of Na^+-K^+ ATPase.[27]

Age-related changes in potassium homeostasis

A number of age-related changes occur in various renal and extrarenal mechanisms for normalization

of serum potassium levels. Increasing age is associated with a gradual deterioration in glomerular filtration rate (GFR) and renal blood flow (RBF), GFR deteriorating by approximately 1 ml/min/year between the fourth and the eighth decade of life.[28] Of more specific relevance to potassium homeostasis is the well-documented decline in distal renal tubular function associated with ageing.[29,30] An impairment in the tubular response to acidosis with increasing age has been well described. The ability to conserve sodium in response to low salt intake is impaired,[29] and the potential for disposal of potassium and acid loads decline with increasing age.[30] The distal convoluted tubule and collecting duct are the sites of control of renal potassium excretion.[31] Therefore, such abnormalities in distal tubular function would render the elderly more susceptible to hyperkalaemia.

Certain age-related neurohormonal changes increase this tendency towards high serum potassium levels. The central role of the renin-angiotensin-aldosterone system to maintenance of normal potassium balance has been emphasized.[13,14,17] Ageing is associated with a decline in plasma renin and aldosterone levels.[32,33] The response of the aldosterone-producing cells in the adrenal zona glomerulosa to a given serum potassium level is conditioned by the simultaneous level of angiotensin II.[14] Depressed renin-angiotensin levels (such as occur with ageing) mean that higher increments in plasma potassium are required to elicit an aldosterone response. Results from our laboratory indicate that a blunted aldosterone response to potassium infusion is found in elderly normal volunteers, in contrast to younger controls.[34]

Ageing is also associated with a rise in circulating levels of atrial natriuretic factor (ANF).[35] ANF is a powerful suppressor of aldosterone secretion both *in vivo* and *in vitro*.[36,37] Moreover, infusion of ANF in healthy young subjects suppresses the response of aldosterone to an acute rise in serum potassium.[38] Thus, the intriguing physiological rise in plasma ANF with increasing age may contribute to the tendency toward hyperkalaemia of older age groups.

Clinical relevance of age-related changes in potassium homeostasis

It is unlikely that these renal neurohormonal changes *per se* would result in hyperkalaemia. An ill-understood but well-described syndrome, hyporeninaemic hypoaldosteronism, is typically a disease confined to older age groups.[39] Typical characteristics include vague symptoms of weakness and syncope, with a tendency to develop cardiac arrhythmia. Laboratory findings include hyperkalaemia, variable degrees of renal impairment and glucose intolerance, unresponsive hyporeninaemia and hypoaldosteronism.[39,40]

Various hypotheses exist regarding the underlying pathogenesis of the syndrome of hyporeninaemic hypoaldosteronism including impaired conversion of prorenin to renin,[41] prostaglandin deficiency[42] and sympathetic nervous system dysfunction in diabetes mellitus.[43] None of these proposals explain the clinical and biochemical features of this syndrome satisfactorily. It seems probable that these and other (as yet unrecognized) factors, superimposed upon age-related changes in renal tubular function,[29,30] plasma renin and aldosterone levels[32,33] and circulating levels of ANF[35–37] may combine to result in the syndrome of hyporeninaemic hypoaldosteronism. End-stage renal failure is very common in the elderly (240/million population over 65 years) as is the incidence of acute renal failure (400/million over 70 years). Both of these conditions are commonly associated with hyperkalaemia.

The predisposition of the elderly to hyperkalaemia also reaches clinical significance when medications which interfere with potassium homeostasis are prescribed to older patients. A large number of drugs, many commonly prescribed, result in potassium retention. Angiotensin-converting enzyme (ACE) inhibitors, e.g. captopril or lisinopril, prevent the conversion of angiotensin I to angiotensin II and thereby reduce aldosterone secretion.[44] Hyperkalaemia is most likely to occur in patients with impairment of renal function, or poor renal perfusion with diminished distal tubular sodium delivery, e.g. congestive heart failure.[45] Clearly, the deterioration in renal function with increasing age[28] combined with other renal and neurohormonal factors[29–38] place the elderly at particular risk of hyperkalaemia, especially in the presence of underlying renal or cardiovascular disease processes.

Similarly, the use of potassium-sparing diuretics is more hazardous in the elderly. Spironolactone is an aldosterone antagonist.[46] Amiloride inhibits distal tubular cell sodium channel permeability, thus interfering with sodium reabsorption, which may influence potassium secretion.[47] Triamterene also appears to inhibit the sodium channel and may inhibit Na^+-K^+ ATPase activity at the basolateral cell membrane.[48]

Recently, trimethoprim, used in high dose to treat *Pneumocystis carinii* pneumonia, was identified as a cause of hyperkalaemia.[49] The proposed mechanism is an effect of trimethoprim which blocks the sodium channel, similar to amiloride (to which it is structurally similar).

Use of non-steroidal anti-inflammatory drugs (NSAIDs) can predispose to hyperkalaemia, especially in the elderly. Deficiency of prostaglandin synthesis has been noted in association with hyporen-

Table 1 Commonly prescribed medications that can cause hyperkalaemia

Drug	Mechanism of hyperkalaemia	Clinical relevance
ACE inhibitors	Suppression of aldosterone secretion	Heart failure with poor renal function
Potassium-sparing diuretics, e.g. Amiloride	Decreased distal tubular potassium secretion	Heart failure with poor renal function or coprescribed with ACE inhibitors
Nonsteroidal anti-inflammatory drugs	Decreased aldosterone and distal tubular potassium secretion	Rheumatoid arthritis with co-existing renal disease
Beta blockers	Promotion of extracellular potassium shift	Ischaemic heart disease in older patients with renal disease
Digoxin	Inhibition of Na^+-K^+ ATPase	Atrial fibrillation in renal failure

inaemic hypoaldosteronism.[42] Likewise, a similar syndrome can be produced iatrogenically by inhibiting prostaglandin synthesis using NSAIDs.[50] Prostaglandins are known to increase distal tubular sodium delivery by inhibiting sodium reabsorption in Henle's loop. This would augment Na-K exchange, and NSAIDs appear to inhibit this occurrence.

Cyclosporine and tacrolimus, immunosuppressant drugs used frequently in transplant recipients, can be associated with hyperkalaemia even in the absence of transplant rejection or impairment of renal function. Hyperchloraemic metabolic acidosis often co-exists. Cyclosporine not only causes hypoaldosteronism, but also direct tubular damage with decreased renal tubular secretion.[51,52]

Lithium toxicity rarely causes hyperkalaemia,[53] apparently by decreasing renal tubular potassium secretion.[54]

Beta adrenergic antagonists can produce hyperkalaemia, predominantly by interference with extrarenal mechanisms of potassium homeostasis.[55] However, impairment of adrenergic function (e.g. in diabetes mellitus)[43] can contribute to diminished renin and aldosterone release. While there is usually a very small increment in serum potassium levels following usage of these agents,[55] caution is warranted in patient with renal failure.[56]

Digitalis intoxication can produce severe hyperkalaemia.[57] The probable mechanism is related to paralysis of the Na^+-K^+ ATPase pump throughout all body tissues. Extracellular potassium rises as intracellular potassium falls, with a resultant predisposition to cardiac arrhythmia. In severe cases, digoxin immune Fab fragment can be life-saving.[58]

These effects are produced by the various agents in all age groups. However, they achieve particular significance in the older patient due, at least partly, to the aforementioned age related physiological changes. These effects are especially likely to occur when two or more agents, e.g. ACE inhibitors and nonsteroidal anti-inflammatory agents, are coprescribed to an older patient, particularly in the presence of relevant pathology, e.g. diabetes mellitus in the above instance. Furthermore, a superadded intercurrent condition, such as myocardial infarction and associated renal hypoperfusion, may result in clinically important hyperkalaemia in the above example. Similar clinically important scenarios are outlined in Table 1.

In conclusion, an age-related decline in renal function associated with alterations in neurohormonal mechanisms predispose the elderly to hyperkalaemia. Hyperkalaemia can be a life-threatening electrolyte abnormality and often becomes clinically relevant following prescription of one or more agents, which raise serum potassium levels, to older patients. Dangerous hyperkalaemia may develop during an episode of intercurrent illness in such patients or in the presence of diseases which interfere with potassium homeostasis, e.g. renal disease. Enhanced awareness of this physiological predisposition of the elderly is required since increasing age is associated with an increase in the incidence of certain disorders and the ingestion of medications which also interfere with potassium homeostasis.

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