Hypothesis

Has potassium been prematurely discarded as a contributing factor to the development of uraemic neuropathy?

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Introduction

Renal failure results in neurological dysfunction due to uraemia, the accumulation of urea and other substances in the blood [1]. This dysfunction may be manifest in the central, autonomic or peripheral nervous systems, with the incidence of peripheral neuropathy estimated to be 60–65% in patients beginning dialysis [2]. Uraemic neuropathy is a distal, symmetric, mixed sensorimotor, predominantly axonal polyneuropathy, affecting legs more than arms [2,3]. The pathological findings are similar to those in other toxic neuropathies and the mechanism of nerve damage is unknown.

The observation that most neurological complications of renal failure can be improved by adequate haemodialysis led to the conclusion that there is a dialysable uraemic neurotoxin, or toxins [4]. The further observation that haemodialysis regimes sufficient to control urea may be inadequate to prevent neuropathy led to the ‘middle molecule’ hypothesis: uraemic neurotoxins have molecular weights in the range 500–2000 Da, so that although they can be removed by dialysis, this occurs more slowly than the removal of small molecules such as urea or creatinine [5,6]. This hypothesis was first proposed in 1965 but remains unproven, and there is still no consensus on what the toxic ‘middle molecules’ might be.

The ‘potassium hypothesis’ of uraemic neurotoxicity

It is well recognized that potassium is one of the most dangerous of the substances that accumulate in the blood during uraemia, because it can be rapidly lethal. If renal failure is uncorrected, and potassium excretion severely compromised, the serum potassium level will build up until, above 7 mM, there is a serious risk of cardiac arrhythmia and fatal cardiac arrest [7–10]. At 7 mM, the potassium equilibrium potential ($E_K$) is shifted by ~12 mV in the depolarizing direction, compared with the normal resting level of potassium (4.5 mM), so that nerve and muscle membranes, with resting potentials largely determined by potassium channels, become dangerously depolarized.

Membrane depolarization first increases excitability, as the threshold potential for spike initiation is approached, but then reduces excitability, as sodium channels become inactivated. The dangers of severe hyperkalaemia are not limited to the heart: neuromuscular function can also fail, so that patients who do not die from cardiac arrest may be afflicted by ascending paralysis [11]. There may also be quadriplegia, areflexia and abnormalities of the cranial nerves [12–14]. Whereas serum potassium concentrations above 7 mM are regarded as constituting a medical emergency, stable concentrations as high as 6 mM (at which...
$E_K$ is depolarized by $\sim 8 \text{ mV}$) may be considered sufficiently safe as not to need therapy, particularly if the electrocardiogram is normal [8].

However, such a rationale may not be entirely without risk, as even moderate hyperkalaemia is likely to have damaging effects on nerve and muscle cells if sustained over long periods, through a depolarizing mechanism. This ‘potassium hypothesis’ of uraemic neurotoxicity follows from the proposition that nerve fibres must maintain adequate membrane polarization and transmembrane ion gradients in order to maintain normal biochemical homeostasis [15].

Nielsen [16] also considered membrane depolarization an important factor in uraemic intoxication, but he attributed this process to block of Na$^+$/K$^+$-ATPase. What constitutes adequate membrane polarization is not known, but recent nerve excitability studies have shown that the degree of axonal depolarization found in many patients with chronic renal failure and mild hyperkalaemia (up to 6.1 mM) is never seen in normal subjects, except after application of a sphygmonanometer cuff to arrest the circulation for several minutes [17,18].

**Potassium meets the criteria for a uraemic neurotoxin**

The following substances have been considered as possible uraemic neurotoxins [1,19–22]: urea, creatinine, guanidine, methylguanidine, guanidinosuccinic acid, uric acid, oxalic acid, phenols, aromatic hydroxyacids, indican, amines, myo-inositol, ‘middle molecules’, $\beta_2$-microglobulin, parathyroid hormone, amino acids and neurotransmitters. There is no compelling evidence for any of these, and recent reviewers have tended either to favour the middle molecule hypothesis [3], for want of a better one, or to regard ‘many or all’ retained metabolites as contributing to neurotoxicity [19]. Surprisingly, these reviews have either ignored potassium, or specifically excluded it from consideration as a possible candidate.

It has been proposed that for a substance to be accepted as a uraemic neurotoxin [1,23,24]: (i) it must be an identifiable chemical; (ii) it should be elevated in the blood of patients with uraemia; (iii) there should be a direct, positive relationship between the blood level and neurological dysfunction; (iv) it should cause neurological dysfunction in experimental animals at appropriate blood levels; and (v) its removal from the blood should abolish the dysfunction. To account for the need for long dialysis times to reduce the incidence of uraemic neuropathy, we can add: (vi) dialysis should remove the substance from the body, but much more slowly than it removes urea.

Applying these criteria, the ‘middle molecule’ hypothesis fails at the first hurdle (i). Some middle molecules have been identified, but none has satisfied criterion (iii), because their neurotoxicity has not been clearly demonstrated [19]. The same lack of clear neurotoxic function applies to nearly all the other compounds listed above. An exception is parathyroid hormone, the level of which in uraemic patients has been correlated with decreased motor nerve conduction velocity [25] and which has a number of other toxic effects [19,24]. However, parathyroid hormone has a molecular weight of 9600 Da and is not dialysable, so it fails criterion (vi).

In contrast, potassium (or excess potassium) satisfies all the criteria for which data are available. Potassium is clearly an identifiable chemical (i). Hyperkalaemia is common in patients with chronic renal failure (ii), and chronic renal failure is much the most important cause of chronic hyperkalaemia. Hyperkalaemia is expected to cause a direct membrane depolarization of nerve and muscle membranes, and this can be demonstrated indirectly in patients with chronic renal failure by nerve excitability testing. Recent studies have established that nerve excitability parameters were significantly correlated with pre-dialysis potassium levels in patients with chronic renal failure [17] and ongoing unpublished observations. The excitability parameters studied for motor axons, which included relative refractory period, supereexcitability and threshold electrotonus measures, were those previously found to provide the best indication of changes in membrane potential [18], and only patients with hyperkalaemia showed evidence of depolarization. In contrast to these findings in uraemic patients, nerve excitability recordings undertaken in a patient suffering acute hypokalaemia found evidence of axonal hyperpolarization, the complete reversal of findings in uraemia patients [26].

Potassium therefore satisfies criterion (iii). The findings in patients with chronic renal failure are also supported in the acute setting, where a single dialysis session with correction of serum hyperkalaemia has been shown to be sufficient to reverse clinical weakness and improve neurophysiological abnormalities, particularly in relation to nerve conduction slowing [27].

Similar tests have not been applied to experimental animals to test criterion (iv), but there is no doubt that high levels of potassium are also neurotoxic to animals. Excitability tests demonstrated that dialysis, which reduces serum potassium, reduces the membrane depolarization of peripheral nerves [17], so that potassium also satisfies test (v). Finally, and most importantly, because $\sim 98\%$ of potassium is intracellular, excess potassium is not removed quickly from the body by dialysis. To abolish hyperkalaemia therefore requires much more dialysis than to remove excess urea. Thus in a study of 14 hyperkalaemic patients, Blumberg et al. [28] found that although plasma potassium was reduced by 4 h of high-flux haemodialysis from an average of 5.65 mM down to 3.62 mM, it recovered to 5.01 mM within 6 h. Over the last hour of dialysis, plasma potassium concentration was unchanged, but potassium was still being removed at 61% of the initial rate. Post-dialysis recovery was most marked in the most hyperkalaemic patient (6.9 → 4.2 → 6.1 mM), for whom the dialysis can have provided only short-lived relief from nerve depolarization. Potassium, therefore, satisfies criterion (vi) despite not being a ‘middle molecule’.
Theoretical dependence of resting membrane potential on potassium ions

If the changes in resting potential ($E_r$) established for chronic renal failure patients were due to hyperkalaemia only, it could be expected that the magnitude of such changes would correspond to the predictions of ionic theory [17]. Using derivations of the Goldman–Hodgkin–Katz constant field theory [29,30], a theoretical expression was derived for the relationship between $E_r$ and external potassium concentration [17]. For comparison, the effects of hyperkalaemia on $E_r$ were also estimated using the dependence of the potential-dependent excitability parameters recorded in uraemic patients on serum potassium, combined with data from studies that established the effects of polarizing currents on these parameters [18]. Regression of multiple parameters of axonal function produced a mean estimated depolarization for an increase in serum potassium from 4.5 to 6mM of 5.3mV. This value was consistent with the 5.6mV depolarization predicted independently by the theoretical expression [17]. These calculations provided further support that hyperkalaemia was the direct cause of the abnormal nerve excitability properties recorded in uraemic patients [17].

Testing the potassium hypothesis

Our evidence that axon depolarization prior to dialysis is related to hyperkalaemia [17] requires confirmation, but a more stringent test that potassium is responsible would be to compare the time course of recovery of serum potassium concentration with the recovery of nerve excitability properties after dialysis. No other substance is expected to show the degree of recovery within 6 h found for potassium [28]. The hypothesis that chronic axonal membrane depolarization leads to neuropathy may be investigated retrospectively in some clinics by comparing pre-dialysis potassium levels, recorded over a period of years, with incidence of neuropathy. This may not, however, prove as straightforward as it sounds. Testing whether uraemic neuropathy is primarily due to hyperkalaemia will be a task comparable with testing whether diabetic neuropathy is primarily due to hyperglycaemia. Prospective studies are, however, currently underway in Sydney monitoring serum potassium levels in uraemic patients and comparing nerve excitability recordings with clinical findings and the presence or development of neuropathy.

The possibility that potassium could also play a role in the development of uraemic encephalopathy is even more problematic. The potassium concentration of the cerebrospinal fluid (CSF) is normally very tightly controlled, in the face of changing serum concentrations [31]. Whereas the blood–nerve barrier appears only to slow equilibration of sodium and potassium concentrations between serum and endoneurial fluid [32], the blood–brain barrier incorporates ion pumps to maintain CSF potassium at a lower level of ~2.8mM. Because of the powerful mechanisms of CSF potassium homeostasis, potassium has been rejected as a cause of uraemic encephalopathy [1]. This may be correct, but the tightness of the normal control of CSF potassium reflects its crucial importance for normal brain function, and little is known of CSF potassium levels in uraemic patients. In acutely uraemic rats, there is a breakdown of the blood–brain barrier and increased influx of potassium into the brain [33], so that in bilaterally nephrectomized rats, CSF potassium rises from its normal value of ~3mM to ~6mM after 32 h, as serum potassium reaches ~10mM [34]. On the other hand, in unilaterally nephrectomized rats, made chronically hyperkalaemic (6.8mM) with a high potassium diet, CSF potassium only increased by 0.1mM [35]. One possibility is that CSF becomes hyperkalaemic only when another uraemic neurotoxin weakens the blood–brain barrier. This could account for the finding that five uraemic patients had significantly raised CSF potassium, even though their serum potassium levels were normal [36]. Uraemic patients may therefore have difficulty in preventing increased levels of serum potassium reaching their brain parenchyma, with consequent deleterious effects on brain function. To test this possibility would require extensive CSF sampling, to evaluate correlations between CSF constituents and EEG or other indices of brain function, comparable with those described by Hughes [37] for serum constituents.

Conclusion

Potassium at high concentrations is already known to be a lethal uraemic neurotoxin, but mild hyperkalaemia has been considered innocuous. Excess potassium, which is removed only slowly from the body by dialysis, fits the profile of the neurotoxin responsible for uraemic neuropathy better than ‘middle molecules’, parathyroid hormone or any other organic substance that has been proposed [19–24]. It is hypothesized that potassium contributes to the process of uraemic neurotoxicity, and that chronic hyperkalaemia, which depolarizes nerve and muscle membranes [38], interferes with mechanisms of ionic homeostasis essential for cellular viability. This hypothesis implies that the achievement of normokalaemia, rather than just the avoidance of severe hyperkalaemia, should become a priority in the treatment of patients with chronic renal failure, especially those with evidence of neuropathy.

Conflict of interest statement. None declared.

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