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Neuropathy, axonal Na^+/K^+ pump function and activity-dependent excitability changes in end-stage kidney disease

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Abstract

Objective: To investigate the mechanisms underlying peripheral neuropathy and to provide insights into axonal Na^+/K^+ pump function in patients with end-stage kidney disease (ESKD).

Methods: Nerve excitability was assessed in 10 ESKD patients before and after a single session of haemodialysis and in 29 age-matched control subjects. Changes in excitability were recorded at baseline and following maximal voluntary contraction (MVC) of abductor pollicis brevis (APB) for 60 s. Serum concentrations of putative neurotoxins including potassium, urea, parathyroid hormone and beta-2-microglobulin were also measured.

Results: Baseline excitability values were consistent with axonal depolarisation prior to dialysis. Following maximal voluntary contraction (MVC), there was an increase in threshold, which was associated with reduced strength-duration time constant and increased superexcitability, consistent with axonal hyperpolarisation. These changes were quantitatively similar for patients and controls, arguing against any significant reduction in the axonal Na^+/K^+ pump in ESKD. Following dialysis, activity-dependent changes were less in ESKD, which suggests greater Na^+/K^+ pump activity prior to dialysis, the opposite of the changes expected with reduced Na^+/K^+ pump function. The reduced post-contraction threshold change in post-dialysis recordings is likely to be secondary to relative hyperpolarisation of the axonal membrane following dialysis and reduction in K^+ concentration.

Conclusions: Our findings suggest that Na^+/K^+ pump function is not impaired in patients with ESKD.

Significance: Pre-dialysis excitability changes in ESKD patients may be explained on the basis of hyperkalaemia. Alteration in Na^+/K^+ pump function does not appear to be a contributing factor to the development of neuropathy in ESKD patients.

Keywords: Membrane potential; Na^+/K^+ pump; Nerve excitability; Potassium; Uraemic neuropathy

1. Introduction

Patients with end-stage kidney disease may develop a length-dependent distal symmetrical polyneuropathy, with prevalence rates that vary from 65 to 100% dependent on diagnostic criteria (Krishnan et al., 2005; Nielsen, 1973; Van den Neucker et al., 1998). Neurophysiological studies typically demonstrate reduction in sensory and motor amplitudes with relative preservation of conduction velocities and distal motor latencies, findings that are

Abbreviations ADH, activity-dependent hyperpolarisation; CMAP, compound muscle action potential; ESKD, end-stage kidney disease; MVC, maximal voluntary contraction; τ_{SD}, strength-duration time constant.

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consistent with a sensorimotor neuropathy of the axonal type (Angus-Leppan and Burke, 1992).

In terms of the pathophysiology of uraemic neuropathy, studies in the 1960s demonstrated that patients treated with peritoneal dialysis have a reduced rate of neuropathy compared to patients on haemodialysis (Babb et al., 1971). These differences were attributed to the wider pore size of the peritoneal membrane which would allow for better diffusion of substances in the middle molecular range of 300–12,000 Da (Vanholder et al., 1994). The concept of a dialysable toxin gained further favour following studies which demonstrated changes in neurophysiological parameters after a single dialysis session (Lowitzsch et al., 1981; Nielsen, 1973).

More recently, studies using excitability techniques, which have provided information regarding axonal ion channel function and membrane potential in a number of neuropathic conditions (Kiernan et al., 2002a; Kitano et al., 2004; Krishnan and Kiernan, 2005; Kuwabara et al., 2002b), have been applied to end-stage kidney disease (ESKD) patients. These studies have demonstrated alterations in membrane potential, specifically axonal depolarisation, prior to haemodialysis, with subsequent improvement in axonal function post-dialysis (Kiernan et al., 2002b; Krishnan et al., 2005). Comparison between levels of serum electrolytes and putative neurotoxins and excitability indices of membrane potential have indicated that the principal cause of membrane depolarisation prior to haemodialysis is hyperkalaemia (Bostock et al., 2004; Kiernan et al., 2002b; Krishnan et al., 2005). However, axonal depolarisation may also be induced through alteration in the function of the electrogenic energy-dependent Na^+/K^+ pump (Bostock et al., 1994; Kiernan and Bostock, 2000; Ritchie and Straub, 1957) and inhibition of the Na^+/K^+ pump by uraemic neurotoxins has been proposed as the mechanism underlying membrane depolarisation in uraemic patients (Nielsen, 1973).

Nerve excitability measurements provide a means of detecting changes in membrane potential caused by activation of the Na^+/K^+ pump (Bostock and Bergmans, 1994; Bostock and Grafe, 1985; Kiernan et al., 2004). Vagg and colleagues (1998) showed that the activity-dependent hyperpolarisation (ADH) of motor axons induced by voluntary activity causes threshold changes that can be used to assess Na^+/K^+ pump function. Abnormalities of ADH have been noted in diabetic neuropathy (Kuwabara et al., 2002a), a condition in which reduced activity of the Na^+/K^+ pump has been suggested (Greene, 1986; Krishnan and Kiernan, 2005). Consequently, the present study recorded excitability parameters before, during and after maximal contraction of abductor pollicis brevis (APB) for 60 s in ESKD patients, to investigate the pathophysiology of uraemic neuropathy and whether alterations in Na^+/K^+ pump function may contribute to the axonal depolarisation that occurs in uraemic patients and thereby the development of neuropathy.

2. Methods

Studies were undertaken in 10 patients with ESKD (6 men, 4 women: age range, 17–69 years) receiving haemodialysis 3 times per week, using a biocompatible low-flux polysulfone membrane (Fresenius, Bad Homburg, Germany). All patients were dialysed against a K^+ concentration of 2 mmol/L. Demographic and clinical data for subjects have been previously presented (Krishnan et al., 2005; see Table 1, subjects no. 1–4, 6–8, 10–12). All subjects were studied on a separate occasion to those previous lower limb studies. None of the patients had a history of other illnesses known to cause neuropathy such as diabetes or amyloidosis and there was no history of exposure to neurotoxic medications, including immunosuppressive therapy. The causes of ESKD in this group were glomerulonephritis (6 patients), polycystic kidney disease (1), medullary cystic kidney disease (1) and hypertensive vascular disease (2). Patients gave informed consent to the procedures, which were approved by the South East Sydney Area Health Service Human Research Ethics Committee (eastern section) and the Committee on Experimental Procedures Involving Human Subjects of the University of New South Wales. The studies were performed in accordance with the Declaration of Helsinki.

The excitability properties of median nerve motor axons were measured before, during and 1 h after a standard 5 h haemodialysis session. Serum levels of electrolytes, urea, creatinine and potential neurotoxins (parathyroid hormone and beta-2-microglobulin) in the middle molecular range (Vanholder et al., 1994), were measured at the time of the excitability studies. In all excitability studies, the median nerve was stimulated at the wrist and the resultant compound muscle action potential (CMAP) was recorded from abductor pollicis brevis using surface electrodes. The active recording electrode was placed over the motor point of APB and the reference was placed 4 cm distally over the proximal phalanx. The amplitude of the CMAP was measured from baseline to the initial negative peak. Skin temperature was monitored close to the site of stimulation for the duration of each study.

The current required to produce the desired CMAP amplitude was determined using a computerized threshold-tracking program (QTRAC version 5.2a, Institute of Neurology, Queen Square, London, with multiple excitability protocol TRONDXM2) that was run by a pentium computer (Kiernan et al., 2000). Recordings were amplified (gain 1000, bandwidth 5 Hz–10 kHz) and digitized using an analog-to-digital (A/D) board (DT2812, Data Translation, Marlboro, Massachusetts), with a sampling rate of 10 kHz.

Baseline excitability parameters were recorded using a previously described protocol (Kiernan et al., 2000). Stimulus–response behaviour using two stimulus durations, threshold electrotonus to 100 ms polarising currents, a current threshold relationship and the recovery of excitability following supramaximal stimulation were recorded.