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Review

Cerebro-renal interactions: Impact of uremic toxins on cognitive function

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ABSTRACT

Cognitive impairment (CI) associated with chronic kidney disease (CKD) has received attention as an important problem in recent years. Causes of CI with CKD are multifactorial, and include cerebrovascular disease, renal anemia, secondary hyperparathyroidism, dialysis disequilibrium, and uremic toxins (UTs). Among these causes, little is known about the role of UTs. We therefore selected 21 uremic compounds, and summarized reports of cerebro-renal interactions associated with UTs. Among the compounds, uric acid, indoxyl sulfate, *p*-cresyl sulfate, interleukin 1-β, interleukin 6, TNF-α, and PTH were most likely to affect the cerebro-renal interaction dysfunction; however, sufficient data have not been obtained for other UTs. Notably, most of the data were not obtained under uremic conditions; therefore, the impact and mechanism of each UT on cognition and central nervous system in uremic state remains unknown. At present, impacts and mechanisms of UT effects on cognition are poorly understood. Clarifying the mechanisms and establishing novel therapeutic strategies for cerebro-renal interaction dysfunction is expected to be subject of future research.

Contents

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1. Introduction

Cognitive impairment (CI) associated with chronic kidney disease (CKD) has received attention as an important problem in recent years. CI accompanied by CKD occurs not only in end-stage renal disease (ESRD) patients but also in patients with early-stage CKD, and CKD is a risk factor for CI development (McQuillan and Jassal, 2010). CI with CKD not only influences daily life and job function, but also results in longer hospitalization and higher risk for mortality. Bugnicourt et al. (2013) estimated a prevalence of CI in CKD of 30% to 60%, a value at least twice that observed in age-matched controls. In Japan, the number of hemodialysis (HD) patients has increased from 116,303 to 304,856 (from 1991 to 2011), and mean age has risen from 55.3 to 66.6 years old (Nakai et al., 2013). Behavioral abnormalities such as restlessness during HD sessions, needle removal accidents, non-compliance with drug regimens, and difficulty with dietary restrictions are all critical issues seen in elderly dialysis patients with dementia.

Cerebrovascular disease, anemia, secondary hyperparathyroidism, dialysis disequilibrium, and uremic toxins (UTs) have been reported as major causes of CI accompanied by CKD (Beard et al., 1997; Brines et al., 2000; Cerami et al., 2001; Chou et al., 2008; Cogan et al., 1978; Drueke et al., 2006; Erbayraktar et al., 2003; Goldstein et al., 1980; Goldstein and Massry, 1980; Guisado et al., 1975; Lee et al., 2004; Leist et al., 2004; Pfeffer et al., 2009; Pickett et al., 1999; Rabie and Marti, 2008; Seliger et al., 2005; Shah et al., 2006; Singh et al., 2006; Temple et al., 1992; Zhang et al., 2009). Uremia can be defined as biochemical and physiologic dysfunction that increases with progression of CKD, resulting in variable symptomatology (Vanholder and De Smet, 1999). Various potentially toxic compounds are accumulated in CKD patients, and these compounds are called "uremic retention solutes". Such solutes that are biologically/biochemically active are called "uremic toxins" (Vanholder et al., 2003a, 2008). One hundred fifty-two UTs have been detected in the past (http://www.uremic-toxins.org/), and these molecules have been shown to have various negative effects, such as anorexia, cardiac failure, anemia, immune dysfunction, malnutrition, inflammation, and skin atrophy (Vanholder et al., 2008). However, the influence of UTs on CI in CKD patients is largely unknown. Therefore, from a collection of 152 known UTs, we selected a subset of 21 compounds reported (in previous research) to exhibit a relationship with the central nervous system (CNS). The present work summarizes the relevant literature for associations between UTs and cerebro-renal interactions.

2. Material and methods

2.1. Review criteria

The information referenced in this paper was compiled by performing MEDLINE searches using the terms "asymmetric dimethylarginine", "guanidino succinic acid", "methylguanidine", "hypoxanthine", "uric acid", "3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid", "hippuric acid", "homocysteine", "indole-3-acetic acid", "spermidine", "putrescine", "methylglyoxal", "leptin", "indoxyl sulfate", "*p*-cresyl sulfate", "interleukin 1-β", "interleukin 6", "tumor necrosis factor alpha", "parathyroid hormone", "beta-2-microglobulin", "cystatin C", "(chronic) kidney disease", and "dialysis" in combination with the terms "cognitive impairment", "dementia", and "brain". Further references were identified by hand-searching reports from recent large clinical trials or innovative basic research for the terms "cerebro-renal interaction" and "uremic toxin". All cited articles were written in English.

2.2. Cognitive impairment in CKD patients

CI accompanied by CKD occurs not only in ESRD patients but also in patients with early-stage CKD, and CKD is considered a risk factor for CI development (McQuillan and Jassal, 2010). Previous studies demonstrated the association of CI and CKD from a variety of perspectives. For example, patients with mild CKD or with albuminuria exhibited declines in memory as well as impairment in concentration and visual attention (Hailpern et al., 2007; Weiner et al., 2009), and CKD was associated with an increased prevalence of CI (odds ratio, 1.23). Patients with estimated glomerular filtration rates (eGFR) of less than 30 mL/min/1.73 m^2 exhibited a more than five-fold elevation in risk for CI (Khatri et al., 2009; Kurella et al., 2005b; Kurella Tamura et al., 2008); CKD was associated with a 37% increased risk of CI over a 6-year follow-up interval. The increased risk of CI associated with a 15-mL/min/1.73 m^2 decline in eGFR was similar in magnitude to the effect of being 3 years older (Buchman et al., 2009; Kurella et al., 2005a; Seliger et al., 2004). In one study, only 13% of HD patients were classified as having normal cognition (Murray et al., 2006). CI accompanied by CKD has effects not only on daily life and job function but also on hospitalization length and increased risk of mortality. The average time to death in HD patients with CI was 1.09 years, and hazard ratio (HR) for death was 1.87, which was higher than that seen in HD patients with cardiac disease (HR, 1.28) or stroke (HR, 1.20) (Rakowski et al., 2006).

Memory holding errors and impaired responses due to frontal lobe dysfunction occur frequently in patients with CI accompanied by CKD (Lee et al., 2011; Post et al., 2010). Cerebrovascular disease, anemia, secondary hyperparathyroidism (SHPT), dialysis disequilibrium, and UTs have been reported as major causes of CI with CKD (Beard et al., 1997; Brines et al., 2000; Cerami et al., 2001; Chou et al., 2008; Cogan et al., 1978; Drueke et al., 2006; Erbayraktar et al., 2003; Goldstein et al., 1980; Goldstein and Massry, 1980; Guisado et al., 1975; Lee et al., 2004; Leist et al., 2004; Pfeffer et al., 2009; Pickett et al., 1999; Rabie and Marti, 2008; Seliger et al., 2005; Shah et al., 2006; Singh et al., 2006; Temple et al., 1992; Zhang et al., 2009). Hypoxia-induced deleterious effects on brain metabolism and/or direct effects on CNS by decreased erythropoietin (EPO) are considered to be mechanisms of CI resulting from renal anemia (Brines et al., 2000; Lee et al., 2004; Pickett et al., 1999; Temple et al., 1992). The ameliorative effects of EPO on cerebral hypoxia or brain tissue damage after trauma are expected to reflect the neurotrophic and neuroprotective effects of EPO; at the same time, EPO may elevate the frequency of vascular events due to increases in hemoglobin levels (Cerami et al., 2001; Drueke