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Chronic renal insufficiency does not induce behavioral and cognitive alteration in rats

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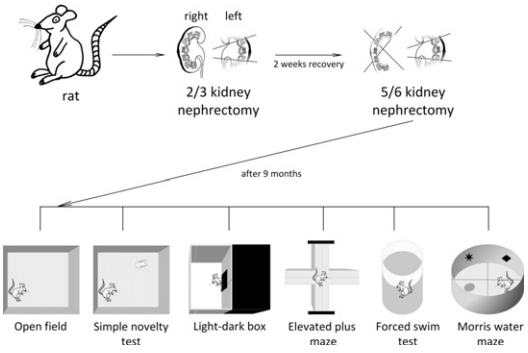
HIGHLIGHTS

- A comprehensive evaluation of behavior was performed in 5/6 nephrectomy rat model of chronic kidney disease
- General locomotion, depression and spatial memory did not change with 5/6 nephrectomy after 9 months
- Anxiety level was more alleviated in nephrectomized rats after nine months
- Psychosocioeconomical traits should be taken into account when assessing behavioral changes in chronic kidney disease patients

GRAPHICAL ABSTRACT



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ABSTRACT

In humans, chronic kidney disease (CKD) is associated with cognitive decline, increase in anxiety, or depression. The underlying mechanisms of these changes remain unclear. The aim of this study was to elucidate whether and how experimentally induced long-term CKD affects cognitive functions in rats.

Thirty male Wistar rats underwent 5/6 nephrectomy (5/6 Nx), an established model of CKD, or sham surgery. Development of CKD was monitored using biochemical analyses and confirmed by renal histology. Behavioral tests of anxiety, depression and spatial behavior were performed before, and at 3 and 9 months after the surgery. CKD in 5/6 Nx rats was characterized by significant decrease of renal function, e.g., glomerular filtration rate, and progressive glomerulosclerosis, tubular atrophy, and interstitial fibrosis; and increased plasma uremic toxins. Mortality was higher in 5/6 Nx rats in comparison with controls. Compared to control group, the surviving 5/6 Nx rats presented similar general locomotor activity, depression traits, and spatial abilities ($p = 0.43$, $p = 0.84$, $p = 0.71$, respectively). At 9 months, lower anxiety in the light–dark box test was observed in 5/6 Nx rats if compared with the control group ($p = 0.02$).

Despite the development of progressive CKD in 5/6 Nx rats, no expected behavioral changes were observed. Further experimental studies associating behavioral responses to severity of CKD are definitely needed to confirm the solely psychosocial aspect background of CKD-associated cognitive impairment in humans.

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1. Introduction

Chronic kidney disease (CKD) is defined as kidney damage resulting in glomerular filtration rate lower than 60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause [1]. Its severity is classified according to glomerular filtration rate (GFR) into 5 stages, those graded IV and V representing the most severe cases. CKD represents a serious public health problem worldwide: increasing incidence and prevalence of CKD imposes burden on the utilization of medical care for CKD itself as well as increase in costs of treating complications from CKD [2]. In humans, one of the most sensitive complications, severely decreasing the quality of life, is the cognitive decline [3,4]. Several studies examining the link between the CKD and cognitive outcomes revealed higher rates of dementia and cognitive dysfunction when compared to those in general population [5,6]. Although the patients with most severe CKD stages are most seriously afflicted, symptoms may manifest also in mild or moderate stages of CKD, and even in subjects with albuminuria without reduced GFR [7,8].

The potential pathogenic factors involved in the development of cognitive disorders observed in humans include increased concentrations of circulating uremic toxins (particularly neurotoxins), pro-inflammatory cytokines, and reactive oxygen species partially released from damaged kidneys [9–11], and changes in serotoninergic and adrenergic neurotransmission [12,13]. Due to the systemic stress, overactivation of sympathetic nervous system may also contribute to the pathogenesis of cognitive development in CKD patients [14]. Cognitive impairment associated with albuminuria may be a consequence of endothelial dysfunction and sub-clinical cerebral microvessel disease [47]. However, the underlying pathological mechanism of cognitive disorders is not very well understood.

Rats in initial stage of CKD are characterized by insignificant decline of creatinine clearance, 3 to 4-fold rise in proteinuria, and mild accumulation of uremic toxins present alterations in activation of neural cells in several brain regions with different functional properties [15]. Observed central sympathetic overactivity, activation of dorsal raphe serotonin-expressing neurons, histamine-expressing neurons in the hypothalamic tuberomamillary nucleus, those in the prefrontal and anterior cingulate cortex and stress-related brain areas and nuclei might be implicated in affecting (among others) attention, memory processing, cognition, learning and synaptic plasticity. However, current experimental studies regarding behavioral changes in CKD show some controversies [16]. For example, in adenine-induced CKD model in rats decrease in motor activity and increase in depression-like behavior were reported [17]. In 5/6 Nx model of CKD, mice exhibited alterations in working memory performance [16]. A different study showed significantly impaired cognitive functions without differences in anxiety between CKD and control mice [18]. Alterations in short-term memory without changes in long-term memory were described in rats with severe CKD induced by subtotal nephrectomy [19]. Different approaches to CKD induction, duration of experiments, and selection of limited number of different tests to study behavioral characteristics of CKD animals do not allow a straightforward comparison of results obtained in different studies.

Herein we aimed to determine the effects of long-term CKD induced in rats by subtotal nephrectomy on a variety of behavioral traits such as locomotor activity, anxiety and depression-like behavior, and memory impairment in a single study.

2. Material and methods

2.1. Animals

Thirty 12-weeks-old male Wistar rats were obtained from Anlab (Prague, Czech Republic). Animals were maintained in 12:12 h light/dark cycle and had *ad libitum* access to water and food throughout the experiments. After arrival, rats were left 2 weeks for acclimatization and handled daily. The room temperature was maintained at 22 ± 1 °C throughout the whole study. All animal experiments were carried out according to Slovak legislation after approval by the institutional ethics committee.

After acclimatization, the animals were randomly assigned into subtotally nephrectomized (5/6 Nx, $n = 15$) and sham operated (CTRL, $n = 15$) groups. The animals in the 5/6 Nx group underwent subtotal (5/6) nephrectomy in two surgical steps as reported previously [20]. Briefly, animals were anesthetized by ketamine/xylazin administered intraperitoneally (100 mg/kg and 10 mg/kg respectively, Richterpharma, Wels, Austria). An incision was made approximately

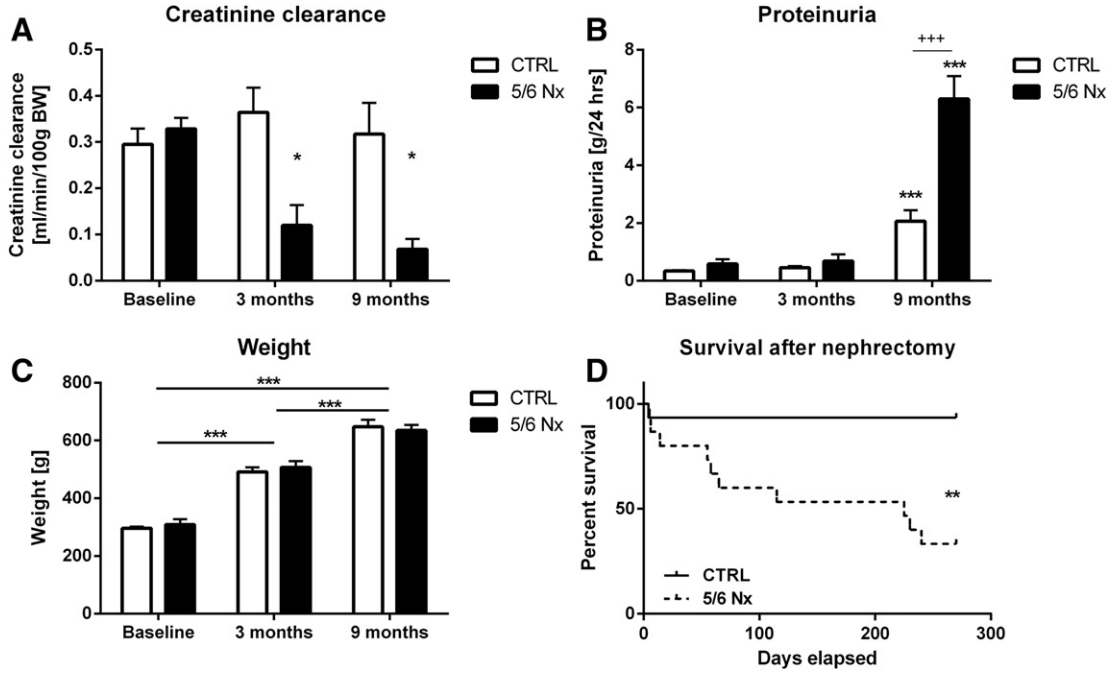

Fig. 1. Physiological panel. (A) Glomerular filtration rate, (B) proteinuria, (C) body weight and (D) survival after nephrectomy measured at baseline and 3 and 9 months after 5/6 nephrectomy. * denotes $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ vs. corresponding CTRL group. Data are presented as mean ± SEM.