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Letter and Reply

Toll-like receptor 4 antagonist and obesity associated kidney disease: Where should we go from here?

To the Editor:

The toll-like receptor (TLR) family plays an important regulatory role in the innate immune system. Several recent studies have demonstrated TLR signaling in the proinflammatory response of a variety of endogenous (lipopolysaccharides, mycoplasma, and lipoproteins) and exogenous (heat shock proteins and saturated and unsaturated fatty acids) stimuli within the kidney. The activation of these proinflammatory pathways is also observed in obesity and associated disorders and plays an exemplary role in causing obesity-associated kidney injury, hypertension, metabolic derangement, and other cardiovascular complications. The study by Min et al [1] evaluated the effect of TLR nonselective antagonist on the progress of kidney disease and metabolic disorders on high fat-fed mice for 12 weeks. The author's remarkable observation was that TLR antagonist treatment decreased urinary excretion of protein, urinary oxidative stress biomarkers, and inflammatory cytokines levels in adipose tissue and kidneys. Very interestingly, extracellular matrix expansion, tubulointerstitial fibrosis which was observed in kidneys on high fat-fed mice was drastically reduced by TLR antagonist treatment. It must be noted that the authors did periodic acid–Schiff staining in the kidney, a marker of extracellular matrix expansion, which was significantly increased with high fat-diet suggesting glomerulomegaly/glomerulosclerosis [2]. The major characteristic feature of obesity-associated kidney disease is increased proteinuria and glomerulomegaly/glomerulosclerosis, which ultimately leads to increase in kidney weight and increased sodium absorption due to the accumulation of renal fat. In this study, however, the authors observed no such increase in kidney weight (in fact a decrease trend in kidney weight was observed), which is really surprising to me. Several authors have demonstrated that perirenal fat compresses and increases the intrarenal pressure within the kidney [3,4]. This increase in pressure impairs the ability of the kidney to excrete sodium in the urine and thus affects pressure natriuresis. I was wondering if the authors got a chance to look at the levels of sodium in the urine samples in their respective animal groups. Did the authors measure glomerular filtration rate, which could have been a better marker to evaluate improvement in kidney function after treating the mice with the TLR antagonist?

Moreover, the authors state that despite eating less food, high fat-fed animals exhibited an increase in body weight, which is amusing. Could the author comment about the calorie content of the diet? How are these animals gaining so much weight? A more interesting observation was that the water intake, for example in ND animals at Week 0 (Table 1 in the original article) was 2.75 mg/d (I strongly believe the unit should be mL/d). Nonetheless, the urine excretion was 375 mL/d. Is it really possible? How on Earth a person can excrete approximately 130 times more than what they drink? This is really unbelievable or, if it was true, the animals would have died before the experiment ended. It appears to be a gross neglect in calculation of the urine volume. This is also true for the rest of the treatment period in all the groups.

Conflict of interest

The author declares no conflicts of interest.

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In Reply:

We appreciate your opinion on our study. As you pointed out, we had indeed provided the wrong units in Table 1. The unit of daily water intake is not mg/d but g/d. The unit of daily water intake is the same as that of daily food intake. In addition, the unit of urine volume is not mL/d but μL/d. We apologize for these mistakes.

Calorie per gram of the high-fat diet (HFD) was higher than the normal chow diet (ND). The calorie of HFD (60% of total calories from fat, 20% from protein, and 20% from carbohydrate) is 5.24 kcal/g [1]. During the study period, total caloric intake of the HFD group was more than the ND (3.84 kcal/g) group. We supposed that high-calorie diet and HFD had a strong influence on the weight gain in the HFD group. However, in terms of kidney weight, it was not entirely clear why decreased kidney weight was observed in mice with HFD-induced obesity. In fact, previous studies reported that HFD did not induce any change in kidney mass [2,3]. We agree that the urine sodium and glomerular filtration rate are excellent markers for kidney function evaluation, especially to understand the mechanisms of increased kidney weight in mice with HFD-induced obesity. However, we could not observe increased kidney weight in this study.

Obesity induces an increased infiltration of activated macrophages into the adipose tissue. Macrophages contribute to the increased secretion of proinflammatory cytokines. Increased levels of proinflammatory cytokines induce systemic inflammation, oxidative stress, and insulin resistance through the activation of immune receptors and stress signaling pathways [4–6]. In our study, gene expressions of proinflammatory and profibrotic cytokines in the kidney tissue tended to increase in HFD mice [7]. Increases in the levels of these cytokines exacerbate renal injury such as glomerular sclerosis, tubulointerstitial fibrosis, and tubule shrinkage. This was believed to be responsible for decreased kidney weight in the HFD group. To determine this point, more studies should be conducted in the future.

We thank you again for your comments. I hope that information presented answers your question.

Conflict of interest

None.

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