Protective effects of green tea polyphenols against renal disease.

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Summary

The effect of green tea polyphenol was examined on nephrectomized rats, a widely used animal model for investigating the progression of glomerular disorders. Green tea polyphenol helps to inhibit the progression of renal failure by scavenging oxidative radicals. In addition, green tea polyphenol ameliorates the state of enhanced oxidation in dialysis patients.

Keywords

Green tea polyphenol, chronic renal failure, dialysis

The background of therapeutic study in renal disease

As renal failure worsens, the concentrations of uremic toxins in the body increase, producing the various signs and symptoms of uremia. Advances in dialysis treatments have now made it possible to remove various uremic toxins from the body efficiently. However, this does not change the morbid condition of the patient, and therefore it is still important to investigate uremic toxins.

Currently known or suspected uremix toxins include small molecules such as methylguanidine (MG), guanidinosuccinic acid (GSA), dimethylamine and myoinositol, intermediate-sized molecules (molecular weight 500-5,000) and large molecules such as β_2-microglobulin (β_2-MG). Among these, MG has long been studied as a likely cause of uremia.

We have previously isolated creatol from urine specimens obtained from patients with chronic renal failure, and have found that the metabolic pathway responsible for the production of MG from creatinine (Cr) *via* creatol is common to all mammals. In addition, creatol, as well as its precursor Cr and its metabolic product MG, accumulate in the blood during chronic renal failure. We have also demonstrated in *in vitro* and *in vivo* experimental systems that, under hydroxyl radical (· OH)-generating conditions, Cr is oxidized to creatol, which in turn is further oxidized to MG *via* the unstable intermediates creatone A and creatone B. The · OH radical is thought to be involved in this reaction, since hardly any creatol is produced in the presence of other active oxygen species.

Injury caused by amidosis has also been reported to be due to active oxygen and free radical activity in hemodialysis patients has therefore been studied from this standpoint. MG is known to be a causal toxin of such diseases as anorexia, gastric ulcer, neuropathy and anemia. As described above, the production of MG is considered to be attributable mainly to · OH. Therefore, renal failure patients seem to suffer a high level of oxidative stress due to an increase in the formation of active oxygen or a decrease in its elimination.

We have carried out extensive fundamental studies aimed at developing new medicaments for renal diseases, focusing on Oriental medicines and medical prescriptions. In the process of these studies, we have found that polyphenol, contained in rhubarb, significantly reverses the decrease in renal function resulting from renal failure. Such improvements in renal function appear to contribute to the amelioration of uremic symptoms in rats. Indeed, we have previously reported the biological activity of this polyphenol, specifically its suppressive effects on blood levels of urea nitrogen, Cr, MG and GSA, in rats with renal failure. Since polyphenol is also contained in large quantities in green tea, it was expected that green tea might have some physiological activity on the kidney that has yet to be recognized. This paper focuses on our recent findings regarding green tea.

Effectiveness of green tea polyphenol in rats with chronic renal failure

To analyse the effects of green tea polyphenol on renal tissue lesions, we focused on the degree of mesangial proliferation and the glomerular sclerosis index. These revealed that renal failure advanced in rats that had undergone excision of part of their kidney volume. Nephrectomized rats receiving oral green tea polyphenol exhibited milder lesions. This effect was more prominent in those given 20 mg of green tea polyphenol than in those given 10 mg. The decrease in creatinine clearance (Ccr) under these renal failure conditions was also significantly reversed after the administration of green tea polyphenol, suggesting that green tea polyphenol inhibited the proliferation of mesangial cells, a phenomenon which became increasingly evident as renal failure advanced, while maintaining the filtering function of the glomeruli.

Yoshida (Yokohama Med. J., 1989) and Ichikawa (J. Jpn. Pediatric Soc., 1989) have pointed out that, following subtotal nephrectomy, growth factors may simultaneously induce glomerular hypertrophy and mesangial proliferation, the former leading to a disorder in the glomerular basement membrane or epithelial cells, resulting in protein leakage, and the latter leading to glomerular sclerosis. Our present study shows that green tea polyphenol suppressed the leakage of urinary protein, suggesting that it delays the progression of glomerular hypertrophy. In addition, the

administration of green tea polyphenol reversed the proliferation of the mesangium in rats with chronic renal failure. It is therefore probable that green tea polyphenol also inhibits the development of glomerular sclerosis resulting from mesangial proliferation as described by Yoshida and Ichikawa.

The uremic toxins that accumulate during renal dysfunction are thought to directly or secondarily affect renal tissue, leading to a further deterioration in renal tissue and function. This produces a vicious circle that results in the terminal stage of kidney disease. In this context, the present study shows that the increases in blood urea nitrogen and serum Cr that usually occur in nephrectomized rats were suppressed by green tea polyphenol. Considering this together with the finding that the renal failure-related accumulation of MG, the strongest currently known uremic toxin, was significantly inhibited by green tea polyphenol, it is possible that green tea polyphenol improves the systemic milieu and breaks the vicious circle, thus inhibiting glomerular deterioration. In other words, the removal of a toxin that affects renal function might have a beneficial effect on the maintenance of cellular function.

The renal failure model produced by partial resection of the renal parenchyma, as used in the present study, results in hypertrophy or swelling of the remaining kidney tissue, with an increase in its weight. On the basis of the fact that the remaining kidney shows significantly increased oxygen consumption and enhanced ATP synthesis, Schrier *et al.* (Am. J. Kidney Dis., 1988) and Harris *et al.* (Am. J. Physiol., 1988) have suggested that free radicals are involved in various ways in the occurrence and progression of renal failure. In the present study, measurement of the antioxidative enzymes involved in the elimination of free radicals such as superoxide and H_2O_2 revealed a significant decrease in superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px) activities, suggesting that the free radical-scavenging system is destroyed in nephrectomized rats. To demonstrate this phenomenon directly, we investigated radical species by spin-trapping with 5,5-dimethyl-1-pyrroline-N-oxide and found that the $\cdot$OH was present in greater amounts in the residual kidney tissue than in normal rat kidney. In contrast, the activities of SOD and catalase were significantly higher in rats given green tea polyphenol after nephrectomy. Since these rats showed weak activity of GSH-Px (an enzyme which, like catalase, eliminates H_2O_2 and which is present in the mitochondrial matrix), we speculate that the site of action of green tea polyphenol is the peroxisome.

Effect of green tea polyphenol in dialysis patients

Cr is frequently used in the clinical setting as a renal function parameter, and is also a precursor in the conversion of creatol to MG. The blood level of this substance was

found to be decreased significantly after 3 months of green tea polyphenol administration, and this effect was maintained until the end of the 6-month administration period. The decrease in the MG level preceded the decrease in Cr, becoming significant after 1 month of green tea polyphenol administration. This level had fallen by 8-10 μg/dl at 5-6 months. This suggests that green tea polyphenol influenced the radicals involved in the production of MG from Cr, in addition to decreasing the amount of Cr. Therefore, we calculated the MG/Cr ratio, and found a significant reduction after 2 months of green tea polyphenol administration. Thus, the radical-scavenging activity of green tea polyphenol was demonstrated in this clinical study, as in previous animal experiments.

Aggressive removal of β_2-MG is desirable in order to prevent the complications of prolonged dialysis, including amyloidosis. In this context, green tea polyphenol caused a significant decrease at every point of measurement during the 6-month administration period, except at 2 months after the start of administration. When the suppressive effect was analyzed in three groups of patients stratified according to their MG levels at the baseline (i.e., by the severity of oxidative stress), a significant fall in β_2-MG was found in the high-MG group during the green tea polyphenol administration period. It was noteworthy that this decrease in β_2-MG occurred despite the use of non-high-performance dialysis, with which it is difficult to eliminate β_2-MG.

We also demonstrated that administration of green tea polyphenol ameliorated pain in the hip, cubitus, coxa and finger in some of them. This suggests that green tea polyphenol inhibits the production of β_2-MG and its deposition in tissue. There were no significant changes in blood pressure, other general laboratory parameters or subjective symptoms during the green tea polyphenol administration period.

Aggressive removal of β_2-MG and suppression of free radical activity are required in order to prevent the complications of prolonged dialysis, including amyloidosis. In this context, green tea polyphenol seems a promising form of treatment. It may also allow the frequency of dialysis to be reduced in some patients. However, research in this field is currently inadequate, and further investigations in a large number of patients are therefore necessary.

References

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