41. GREEN TEA CATECHINS INTERACTION WITH ORGANIC CATION TRANSPORTERS IN RAT KIDNEY

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Green tea is one of well-known beverages in the world. It made from the leaves of *Camellia sinensis*. Green tea extract (GT) and its constituents exerted several biological activities, including anti-cancer, hepato-protective, and anti-oxidant actions. According to the advantage of green tea catechins, it is recently used as dietary supplement. The previous study had shown that GT inhibited estrone sulfate uptake mediated by human organic anion transporting polypeptide (OATPs). Epigallocatechin-3-gallate (EGCG), a major catechins derivative, decreased expression and functions of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Moreover, GT and EGCG increased whereas myricetin, caffeine and catechin decreased the uptake of a prototypical organic cation, 1-methyl-4-phenylpyridinium (MPP^+), into human intestinal Caco-2 cells. However, the interactions of green tea catechins with organic cation transporters (OCTs) have not been yet investigated. The present study was to evaluate the interactions of GT and its catechins on organic cation transport in rat kidney. The uptake of [^{3}H] MPP^+ was measured in intact rat renal cortical slices and second segment of the renal proximal tubule (S2) cells stably expressing rat organic cation transporter 2 (S2-rOct2) in the presence of GT and its catechins. The results showed that GT and ECG could inhibit transport of [^{3}H] MPP^+ in a concentration-dependent manner with the IC_{50} values of 2.7 mg/ml and 0.87 mM, respectively, in rat renal slices and 1.85 mg/ml and 1.67 mM, respectively, in S2-rOct2. The inhibition of MPP^+ uptake had been eliminated after the removal of GT and ECG from the bath solution, suggesting the reversible inhibition by GT and ECG in kidney. As the IC_{50} values were higher than the plasma concentration of catechins in daily tea drinking or supplement, this very weak interaction of GT and its catechins with renal organic cation transporter 2 (OCT2) indicates that the consumption of green tea beverage or catechins supplements does not interfere with therapeutic organic cationic drugs that secreted via OCT2 in kidney.

42. Zotepine 及び Chlorprothixene が持ちうる血中尿酸濃度低下作用及びその機作に関する考察

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【背景・目的】Zotepine と Chlorprothixene は抗精神薬病薬であるが，血中尿酸濃度を下げる効果も知られている．しかし両薬剤の血中尿酸降下作用の詳細な機序は不明であった．

現在判明している薬剤性の血中尿酸濃度低下機序として，近位尿細管における尿酸再取り込み阻害作用と，Xanthine Oxidase（以下，XO）阻害作用がある．そこで，我々は Zotepine と Chlorprothixene の尿酸再取り込み阻害効果と XO 阻害効果について検証した．

【方法】HEK293-URAT1 発現細胞と HEK293-mock 細胞を 24well プレートにて培養し，^{14}C ラベル尿酸と Zotepine および Chlorprothixene それぞれの混和物を well 毎に投与する．^{14}C ラベル尿酸の細胞内への取り込み量をシンチレーションカウンターにて計測する．

XO による尿酸生成反応時に産生された H_2O_2 を用い，蛍光色素を作成する．その吸光度を測定し，そこから XO 活性を算定する．

【結果】^{14}C ラベル尿酸のアップテイク実験では Zotepine と Chlorprothixene を投与した場合，濃度依存的に ^{14}C ラベル尿酸の取り込み量が減少していた．このことから，Zotepine と Chlorprothixene には濃度依存的な尿酸取り込み阻害作用が有ると確認された．

XO 阻害実験では Zotepine および Chlorprothixene を 50 μM 投与した所，XO 活性が 80% 以上維持されている事が確認でき，かつさらなる高濃度下に於いても活性低下は僅かであった．

【考察・結論】Zotepine，Chlorprothixene ともに URAT1 に対する尿酸取り込み阻害作用が確認された．しかし Zotepine，Chlorprothixene ともに XO 阻害は極めて弱いとの結果がでた．

以上の結果より，Zotepine，Chlorprothixene による血中尿酸降下作用は URAT1 の尿酸再取り込みに対する阻害作用による可能性が高いと考えられた．