**P2-75**  Inhibition of the organic cation transporter2 function by green tea catechins

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Green tea extract and its constituents have exerted several biological activities. According to the several advantages of green tea catechins, it is recently utilized as dietary supplement. The previous study had shown that green tea extract (GT) and epigallocatechin-3-gallate (EGCG) increased a typical cationic compound, 1-methyl-4-phenylpyridinium (MPP+), transport into intestinal Caco-2 cells. However, the direct interaction of green catechins with organic cation transporters (OCTs) has not yet been investigated. The present study was to evaluate the interaction of green tea catechins with a major basolateral OCT in kidney, OCT2, using intact rat renal cortical tissues and the second segment of renal proximal tubule (S2) cells stably expressing human or rat OCT2 (S2-h.OCT2/S2-r.OCT2) as study model. GT and epicatechin-3-gallate (ECG) inhibited OCT2-mediated MPP+ transport with IC50 values higher than 1 mg/ml and 1 mM, respectively, which quite higher than the plasma concentration of catechins in daily tea consumption. In addition, this GT inhibitory effect was not due to equivalent catechins compositions. Thus, consumption of green tea beverage or catechins might not interfere with therapeutic organic cationic drugs that secreted via OCT2 in kidney.

**P2-76**  Sepsis accelerates cell cycle transition of proximal tubules in the ultra-early phase as a compensative system

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Acute renal tubular necrosis is a well-known pathological change in acute kidney injury (AKI). The death of tubular cells stimulates the proliferation of neighboring survived tubular cells to recover total tubular function. However, recent studies revealed that AKI concomitant with sepsis does not show characteristic tubular cell death. It has not been examined whether septic AKI accelerates cell proliferation or not. In the present study, we examined the time-course changes in tubular cell proliferation after sepsis. Fucci mice (8 weeks old) that express mCherry at G1 phase showed decrease in the numbers of G1-phase cell in the ultra-early phase (~2h) of sepsis. The rapid cell cycle transition was confirmed by Ki67 or tyrosine analogue staining only in young mice (~12 weeks), not in old mice (~14 months). Toposide, an anticancer drug, abolished the increase in proliferation in young mice. Importantly, old mice or etoposide-treated young mice showed severer AKI than young mice did. These results indicate the tubular cell proliferation without significant cell death in sepsis, possibly as a compensative mechanism against the development of AKI. The cell senescence might disrupt this mechanism and increase the AKI risk.

**P2-77**  Sex difference in protective effect of endothelin receptor antagonist on ischemia/reperfusion-induced acute kidney injury

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Endothelin (ET)-1/ET3 receptor system has been shown to play an important role in the pathogenesis of ischemia/reperfusion-induced acute kidney injury (IAKI). In IAKI of rodent models, there are consistent findings that females are more resistant to the renal injury than males. In the present study, we examined the effects of ABT-627, a selective ET3 receptor antagonist, on IAKI, using male and female Sprague-Dawley rats. IAKI was achieved by clamping the left renal artery and vein for 45 min followed by reperfusion, 2 weeks after contralateral nephrectomy. Renal dysfunction and histological damage were observed 1 day after reperfusion in both male and female rats, although these renal injuries were more marked in male rats than in female rats. Intravenous bolus injection of ABT-627 (1 mg/kg) 5 min before ischemia markedly attenuated IAKI in male rats, but not in females. The sex difference in IAKI was abolished by ovariecotomy and ABT-627 administration attenuated IAKI in ovariecotimized female rats. These findings suggest that ET-1/ET3 receptor system is contributive to the sex difference in the pathogenesis of IAKI.

**P2-78**  Pathogenic activation of TRPC6 channel associated with familial focal segmental glomerulosclerosis (FSGS) mutations may be counteracted by the cGMP/PKG pathway through interaction with actin cytoskeleton

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TRPC6 channel mutations in podocytes induce proteinuria resulting in a progressive kidney failure, FSGS. We studied the abnormal functionality of murine FSGS-related TRPC6 mutations near the N-terminal ankyrin repeats in heterologous expression system with Ca2+ imaging and patch clamp techniques. These mutations enhanced receptor responses to carbachol, whereas showed various mechanosensitivity. These changes were abolished by cytochalasin D which disrupted the cytoskeletal actin filaments. Coimmunoprecipitation experiments indicated that physical interaction between actin and wild-type TRPC6 protein was enhanced by receptor and mechanical stimulations. Pretreatment with 8Br-cGMP, an analogue of cGMP which has been reported to negatively regulate wild-type TRPC6 channel via PKG activation, attenuated both the receptor and mechanical responses of FSGS mutants and their interactions with the actin cytoskeleton. It is thus speculated that activation of the cGMP-PKG pathway may counteract the abnormal activities of FSGS mutants, whereby to protect podocytes from degeneration by mitigating excessive Ca2+ influx through TRPC6 channel.