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Adrenocorticotropic hormone ameliorates acute kidney injury by steroidogenic-dependent and -independent mechanisms

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Adrenocorticotropic hormone (ACTH) has a renoprotective effect in chronic kidney disease; however, its effect on acute kidney injury (AKI) remains unknown. In a rat model of tumor necrosis factor (TNF)–induced AKI, we found that ACTH gel prevented kidney injury, corrected acute renal dysfunction, and improved survival. Morphologically, ACTH gel ameliorated TNF-induced acute tubular necrosis, associated with a reduction in tubular apoptosis. While the steroidogenic response to ACTH gel plateaued, the kidney-protective effect continued to increase at even higher doses, suggesting steroid-independent mechanisms. Of note, ACTH also acts as a key agonist of the melanocortin system, with its cognate melanocortin 1 receptor (MC1R) abundantly expressed in renal tubules. In TNF-injured tubular epithelial cells *in vitro*, ACTH reinstated cellular viability and eliminated apoptosis. This beneficial effect was blunted in MC1R-silenced cells, suggesting that this receptor mediates the anti-apoptotic signaling of ACTH. Moreover, ACTH gel protected mice against cecal ligation puncture–induced septic AKI better than α-melanocyte-stimulating hormone: a protein equal in biological activity to ACTH except for steroidogenesis. Thus, ACTH has additive renoprotective actions achieved by both steroid-dependent mechanisms and MC1R-directed anti-apoptosis. ACTH may represent a novel therapeutic strategy to prevent or treat AKI.

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Acute kidney injury (AKI) is a complex and heterogeneous disease entity characterized by an abrupt loss of kidney function that could be ascribed to numerous causes. In the past 30 years, although progress is indeed being made in identifying biomarkers for early diagnosis of AKI,[1–3] management of AKI is still largely limited to general supportive measures;[4,5] no specific intervention that either prevents or treats the injured kidney or improves survival has been successfully developed.[6] It is imperative to develop a novel, effective, and pragmatic approach to prevent kidney injury or to promote kidney repair and regeneration.[7]

Adrenocorticotropic hormone (ACTH) is an important component of the hypothalamic–pituitary–adrenal axis.[8,9] In the 1950s and the early 1960s, ACTH was widely used for the treatment of lipoid nephrosis.[9–11] Recent clinical and experimental evidence suggests that ACTH has a renoprotective effect in chronic kidney diseases.[9,11,12] Besides governing steroidogenesis, ACTH is also an important physiological agonist of the melanocortin system.[9,13] This system comprises multiple components, including five class A guanine nucleotide–binding protein (G protein)–coupled melanocortin receptors (MCRs) MC1R∼MC5R; endogenous antagonists; and peptide agonists derived from the anterior pituitary gland, including α-melanocyte-stimulating hormone (MSH), β-MSH, γ-MSH, and ACTH.[9,13] Accumulating data demonstrate that melanocortins,[14] in particular α-MSH[15] and its synthetic mimetics,[16] possess a potent protective activity in acute injuries in multiple organ systems,[17–19] including the kidney.[15] Nevertheless, although α-MSH has similar MCR agonizing potency as its parent molecule ACTH,[9,13] the effect of ACTH on AKI has been barely investigated. This study examined the effect of ACTH gel (HP Acthar Gel, Questcor Pharmaceuticals, Hayward, CA), which is an FDA-approved formulation of natural porcine ACTH, on a rat model of AKI induced by tumor necrosis factor (TNF)[20–22] and a murine model of septic AKI induced by cecal ligation puncture (CLP).[16,23,24] We found that ACTH has a kidney-protective effect on AKI that is mediated by both steroid-dependent and -independent mechanisms.

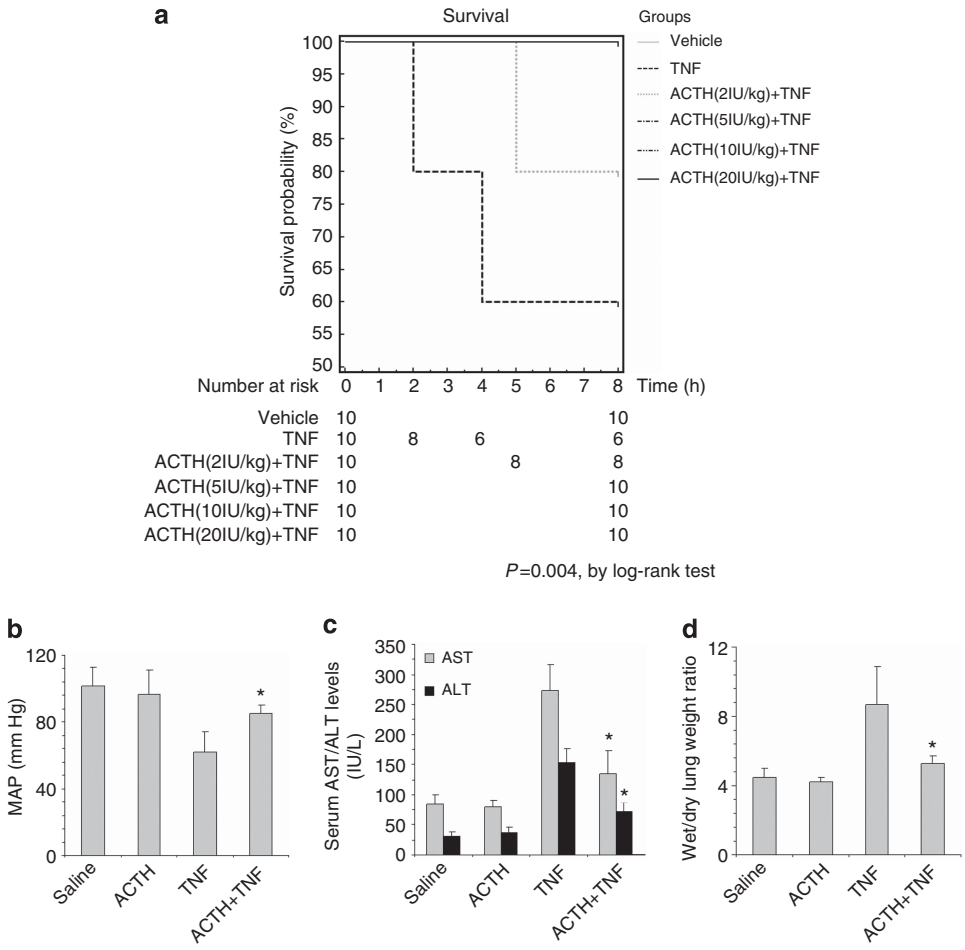

Figure 1 | Adrenocorticotropic hormone (ACTH) gel treatment significantly improves survival and ameliorates systemic organ injury in tumor necrosis factor (TNF)–injured rats. (**a**) Rats were pretreated subcutaneously with saline or ACTH gel at indicated doses 60 min before intravenous bolus injection of recombinant rat TNF (2 mg/kg wt). Rats were evaluated hourly and survival was recorded. Survival rate was plotted against the time course. The survival probability of rats receiving different treatment was determined by Kaplan–Meier survival analysis. $P = 0.0040$ among the groups by log-rank test. (**b**–**d**) Rats were pretreated subcutaneously with saline or ACTH gel (10 IU/kg) 60 min before intravenous bolus injection of recombinant rat TNF (2 mg/kg wt). (**b**) Mean arterial pressure (MAP) was measured and rats were killed 8 h later. (**c**) Blood was collected and serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured to assess acute liver injury. (**d**) Lung was excised and wet to dry lung weight ratio was determined to assess acute lung injury. *$P < 0.05$ versus TNF-alone-treated group ($n = 5$).

RESULTS

ACTH gel improves survival of rats with TNF-induced systemic organ injury

TNF is a pleiotropic prodeath and proinflammatory cytokine involved in the pathogenesis of multiple organ dysfunction and systemic inflammatory response syndrome.[20,21] A single injection of exogenous recombinant TNF immediately disturbed systemic homeostasis and resulted in 40% mortality within 8 h (Figure 1a). ACTH pretreatment reduced mortality and markedly improved general survival in a dose-dependent manner: even at low doses (2 IU/kg), pretreatment with ACTH increased survival to 80%; at higher doses, ACTH treatment resulted in 100% survival from TNF stimulation (Figure 1a), suggesting a general beneficial effect of ACTH. To determine whether ACTH gel therapy has a systemic beneficial action, mean arterial pressure (MAP) was measured and the injury of the liver and lung was assessed. TNF injection induced a profound drop in MAP and caused a hypotensive shock (Figure 1b). Furthermore, TNF elicited acute liver injury as evidenced by the elevated serum levels of hepatic enzymes including aspartate aminotransferase and alanine aminotransferase. TNF also augmented wet to dry lung weight ratios, in agreement with the formation of acute pulmonary edema. ACTH gel treatment (10 IU/kg) significantly corrected the blood pressure, lowered serum aspartate aminotransferase and alanine aminotransferase levels (Figure 1c), and normalized wet to dry lung weight ratios (Figure 1d), signifying a general improvement in hemodynamics and systemic organ injury.

ACTH attenuates kidney injury and dysfunction in TNF-injured rats

To examine the effect of ACTH on TNF-induced kidney injury and to determine the minimal dose of ACTH gel that