COMBINED EFFECT OF DEHYDRATION, HYPERTENSION, AND AGE ON RENAL FRAILTY

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Background and Aims: Renal frailty (RF) is a premorbid and, at least partly, modifiable condition arising from diminished renal functional reserve and defective adaptive response capacity predisposing to acute kidney injury (AKI). RF ensues from subclinical wear or distortion of the renal haemodynamic and tubular homeostatic responses that defend the renal excretory function from supervening circumstances (i.e., stressors such as drugs). In this work, we aimed to study the impact of RF generated by the combined effect of the hydration state, hypertension and ageing on the nephrotoxicity developed by a low dose of cisplatin in the rat.

Method: Young Wistar rats, young spontaneously hypertensive rats (SHR), and aged Wistar rats were used. Rats in each group were randomly subject to four experimental conditions:
- Control: rats with ad libitum water intake, receiving vehicle (0.9% NaCl, i.p).
- Cisplatin: rats with ad libitum water intake, treated with 2.5 mg/kg, i.p. cisplatin.
- Water deprivation: rats deprived of water for 48 h, treated with vehicle (0.9% NaCl, i.p.).
- Water deprivation + cisplatin: rats deprived of water for the 48 h prior to 2.5 mg/kg i.p. cisplatin administration.

Tail vein blood and 24-hour urine samples were collected at basal time (B), after water deprivation (D0), and 4 days after cisplatin/vehicle administration (D4, day of maximum kidney damage). Haematocrit was measured and plasma osmolality, plasma creatinine (Jaffe reaction) and urea (Jung method) concentrations were determined. Urine samples were analysed for volume (urinary flow), osmolality, and proteinuria (Bradford method). Body fluid composition was measured by bioimpedance spectroscopy with an ImpediVETTM VetBIS1 device.

Results: All rats showed clear signs of dehydration after 48 hours of water deprivation: weight loss, increases in plasma osmolality and haematocrit (more pronouncedly in young Wistar and SHR than in aged animals), and reduced flow of a highly concentrated urine (i.e., with elevated osmolality). Bioimpedance analysis revealed a parallel loss of intracellular and extracellular water and net loss of total body water (explaining most of weight loss), with no changes in the liquid distribution between the intracellular and extracellular compartments. Dehydration was reverted after 4 days of rehydration in vehicle-treated rats, and no alteration of renal function was observed due to water deprivation. Administration of cisplatin in young, normohydrated Wistar rats showed minimal loss of renal function that was not worsened by water deprivation. Hypertensive rats showed completely normal renal function when cisplatin was administered under normohydration. Interestingly, however, dehydrated SHR did suffer a cisplatin-induced AKI (significant increases in plasma creatinine, plasma urea and proteinuria). In aged Wistar rats, cisplatin compromised renal function (as supported by increases in plasma creatinine and urea concentration), and this effect was significantly amplified by water deprivation.

Conclusion: This study suggests that dehydration in fully competent young rats is not in itself a significant risk factor for AKI, while the combination of dehydration and hypertension in young rats significantly increases the risk of AKI. Furthermore, ageing poses animals in a state of frailty that renders their kidneys unable to respond to stressors (such as a low dose of cisplatin). Frailty is boldly worsened in dehydrated aged animals. In perspective, models reproducing conditions of increased vulnerability to AKI provide useful tools to search for biomarkers pre-emptively predicting undesired health outcomes before exposure to stressors, and for developing preventing strategies. This study was supported by Project PI21/01226, funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union, and a grant from the Consejería de Educación, Junta de Castilla y León (JES160P20), Spain, co-funded by FEDER funds. Noelia Diaz-Morales is recipient of a Juan de la Cierva-Formación postdoctoral contract (FJC2020-043205-I) funded by MCIN/AEI/10.13039/501100011033 and European Union "NextGenerationEU/PRTR".