Renal targeting potential of a polymeric drug carrier, poly-L-glutamic acid, in normal and diabetic rats

Hann-Juang Chai1
Lik-Voon Kiew1
Yunn Lin Chin1
Anwar Noraziz2
Suzita Mohd Noor2
Yoke-Lin Lo3,4
Chung-Yeng Looi1
Yeh-Siang Lau1
Tuck-Meng Lim5
Won-Fen Wong6
Nor Azizan Abdullah1
Munavvar Zubaid Abdul Sattar7
Edward J Johns8
Zamri Chik1
Lip-Yong Chung3

1Department of Pharmacology, 2Department of Biomedical Science, 3Department of Pharmacy, Faculty of Medicine, University of Malaya, 4School of Pharmacy, International Medical University, Kuala Lumpur, 5Department of Chemical Science, Faculty of Science, Universiti Tunku Abdul Rahman, 6Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, 7School of Pharmaceutical Sciences, Universiti Sains Malaysia, 8Minden, Malaysia, 9Department of Physiology, University College Cork, Cork, Republic of Ireland

Background and purpose: Poly-L-glutamic acid (PG) has been used widely as a carrier to deliver anticancer chemotherapeutics. This study evaluates PG as a selective renal drug carrier.

Experimental approach: 1H-deoxyctydine-labeled PGs (17 or 41 kDa) and 1H-deoxyctydine were administered intravenously to normal rats and streptozotocin-induced diabetic rats. The biodistribution of these compounds was determined over 24 h. Accumulation of PG in normal kidneys was also tracked using 5-(aminooctetamido) fluorescein (fluoresceinyl glycine amide)-labeled PG (PG-AF). To evaluate the potential of PGs in ferrying renal protective anti-oxidative stress compounds, the model drug 4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride (AEBSF) was conjugated to 41 kDa PG to form PG-AEBSF. PG-AEBSF was then characterized and evaluated for intracellular anti-oxidative stress efficacy (relative to free AEBSF).

Results: In the normal rat kidneys, 17 kDa radiolabeled PG (PG-Tr) presents a 7-fold higher, while 41 kDa PG-Tr shows a 15-fold higher renal accumulation than the free radiolabel after 24 h post injection. The accumulation of PG-AF was primarily found in the renal tubular tissues at 2 and 6 h after an intravenous administration. In the diabetic (oxidative stress-induced) kidneys, 41 kDa PG-Tr showed the greatest renal accumulation of 8-fold higher than the free compound 24 h post dose. Meanwhile, the synthesized PG-AEBSF was found to inhibit intracellular nicotinamide adenine dinucleotide phosphate oxidase (a reactive oxygen species generator) at an efficiency that is comparable to that of free AEBSF. This indicates the preservation of the anti-oxidative stress properties of AEBSF in the conjugated state.

Conclusion/Implications: The favorable accumulation property of 41 kDa PG in normal and oxidative stress-induced kidneys, along with its capabilities in conserving the pharmacological properties of the conjugated renal protective drugs, supports its role as a potential renal targeting drug carrier.

Keywords: carboxylated polymers, carboxylated polypeptides, carrier, diabetes, renal drug delivery, acute kidney injury, chronic renal failure, end-stage renal failure

Introduction

Renal failure is a serious health problem throughout the world.1,2 Acute kidney injury as a result of abrupt insults to the kidneys carries considerable morbidity and mortality.3,4 Furthermore, chronic renal failure secondary to other chronic diseases, such as type 2 diabetes mellitus, may gradually progress to end-stage renal failure requiring renal replacement therapy. The economic burden placed by renal diseases on the health care system has been escalating in recent years.5

The pathophysiological basis of acute kidney injury or chronic renal failure has drawn great attention. Various renoprotective compounds have been assessed for their ability to improve renal function.9,10 Poor solubility in plasma, a lack of specific