ACTA MEDICA TRANSILVANICA December26(4):53-55
DOI: 10.2478/amtsb-2021-0074
Online ISSN 2285-7079

SOME MODELS OF CHRONIC KIDNEY DISEASE INDUCED IN THE EXPERIMENTAL ANIMAL

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Keywords: *chronic kidney disease (CKD), tubulo-interstitial fibrosis (TIF)*

Abstract: *Chronic kidney disease (CKD) is one of the clinical features characterized by progressive and irreversible loss of renal function. The incidence of this pathology is constantly increasing globally, due to the growing number of patients diagnosed with diabetes and hypertension, both diseases generating tubular fibrosis and kidney dysfunction. Through experimental models for the production of tubulo-interstitial fibrosis (TIF), we try to understand deeply and comprehensively the main pathogenic mechanisms that govern the onset, progression and worsening of CKD. Understanding the mechanisms underlying the production of this pathology, one can try therapeutic methods to produce an evolutionary slowdown in CKD and also translate the main benefits in clinical practice, based on these experimental models of basic research.*

INTRODUCTION

According to clinical guidelines, CKD in human subjects is defined by the presence of structural and functional abnormalities over a period of more than 3 months and is staged based on the estimation of glomerular filtration rate (GFR) and albuminuria.(1) The prevalence of this pathology is constantly increasing worldwide, reaching an average of 12% of the world's population.(2) Due to these alarming statistics, the evolution of the costs borne by health systems is also increasing rapidly. Therefore, it is necessary to recalibrate the therapeutic methods of preserving renal function that are more effective from a pharmacoeconomic point of view, to change public health policies by relocation of financial resources and to focus on prevention, with coherent education policies, including changes in the lifestyle of patients with risk factors for the development of CKD.(3)

AIM

This paper focuses on the analysis of various methods of inducing the phenomena of tubulo-interstitial fibrosis (TIF), responsible for the progressive deterioration of renal function in experimental animals, small and medium-sized rodents (mice, rats) being considered in this article. Their use has several clear advantages: minimal costs, availability, short lifespan, fast results, metabolic disorders similar to human subjects with CKD.(4) These are the main reasons why these animals are found in most fundamental research articles. The aim is to create experimental patterns that simulate this type of disease as close as possible to reality, in order to facilitate the understanding of the subsidiary mechanisms in such a complex pathological context.

MATERIALS AND METHODS

The present study is based on a systematic analysis of the results identified in the literature, emphasizing the type of method, its description, the algorithm followed from a technical point of view. The main experimental models of TIF, responsible for the development of CKD, are listed. There are experimental models that are based on the use of surgical techniques, respectively models that are based on the use of drugs, both methods having the same impact on the kidney, respectively the induction of fibrosis phenomena, which triggers the installation of CKD.

RESULTS

In the present study we focused only on some experimental models that underlie the onset of renal fibrosis, responsible for the production of CKD. TIF is much more complex than initially considered, recent studies proving that it also occurs in glomerular disease. Therefore, even diabetes and hypertension are associated with tubular fibrosis. Of course, there are advantages and disadvantages of these CKD models in the experimental animal, so the model that best satisfies the working hypotheses taken into account in the context of a fundamental research must always be chosen. If surgical models are considered, then we cannot avoid the most popular model, the 5/6 nephrectomy that mimics CKD in humans, by loss of kidney mass. In this model, glomerulosclerosis phenomena appear in a first phase, followed by TIF and tubular atrophy.(4,6)

Another popular model is related to the induction of interstitial fibrosis phenomena by unilateral ureteral obstruction. In this case there is the advantage of using the contralateral kidney as a control, but at the same time we must know that we will not see changes in nitrogen retention products or protein loss through the renal filter.(7)

Unilateral ligation of the renal vein is another method that uses surgical techniques to achieve the goal, represented by renal dysfunction. It is a technique that does not involve special costs, with a low impact on the status of the experimental

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Article received on 23.10.2021 and accepted for publication on 02.12.2021

animal.(8,9) We mention the fact that the animals after the surgery will be placed in spaces where a constant temperature of 25 degrees Celsius is ensured, a 12-hour day/night cycle and food and water ad libitum (table no. 1).

Animal models in which CKD induction medication is administered, presented above, may sometimes be preferred because they are not as invasive as models that require certain surgical techniques and may simulate CKD as well. Choosing the animal model that best meets the requirements of the investigator is a real challenge. Cisplatin, folic acid exerts toxicity in the renal tubule (10), streptozocin is a good marker for the simulation of diabetic nephropathy by tubular and glomerular impairment in type 1 diabetes (11) and adriamycin is chosen for the simulation of glomerular nephropathy.(12)

Another advantage of these substances is their intraperitoneal administration, the only exception being adriamycin. These animals will also be provided with a constant temperature of 25 degrees Celsius, 12-hour day / night cycles, water and food ad libitum (table no. 2).

Table no. 1. Surgical Models

TYPE OF METHOD	DESCRIPTION	ANIMAL MODEL	TIME OF INDUCTION
Unilateral Ureteral Obstruction	Sterile conditions are ensured, in the first stage the anesthesia of the experimental animal is ensured, then a median laparotomy is performed. The left ureter is isolated, two ligatures are made, between the renal pelvis and the bladder, and sectioned between them, producing hydronephrosis, tubular injury and cell death. Subsequently, the surgical incision is carefully sutured and the experimental animal is relocated to recover from anesthesia. Males are preferred, because the reproductive organs of females complicate the surgical technique.(8,13,14)	Mouse; Rat	14 days
Nephrectomy 5/6	Sterile conditions are ensured, in the first stage the anesthesia of the experimental animal, then an incision is made at the level of the right flank, in order to expose the right kidney. The adrenal gland, together with the renal capsule is carefully dissected, then 2/3 of the right kidney, respectively the upper pole and the lower pole are excised. The second stage is performed after a week, begins with anesthesia of the animal and consists of an incision in the left flank, followed by nephrectomy, after removal of the adrenal gland.(8,14,15)	Mouse; Rat	28 days
Unilateral Renal Vein Ligature	Sterile conditions are ensured, in a first stage the anesthesia of the experimental animal is performed. An incision is made in the left flank, through which the left renal vein is exposed and ligated. The incision is then sutured, with a reduced operating time of about 20 minutes. In female rats, the right renal vein approach is preferred, because at this level the ovarian vein is dependent on the inferior vena cava and not the renal vein, as is the case on the left side.(8,9)	Rat	10 days

Table no. 2. Drug Models

TYPE OF METHOD	DESCRIPTION	ANIMAL MODEL	TIME OF INDUCTION
Cisplatin	Cisplatin is a nephrotoxic drug used in medical practice as an antineoplastic. There are CKD patterns created by intraperitoneal injection of cisplatin at 2-week intervals, which show significant renal dysfunction installed by decreased RFG, as a result of the toxic action exerted by this drug on the tubular epithelium.(16,17)	Mouse; Rat	14 days
Streptozocin	Streptozocin is an antineoplastic agent, in the class of alkylating agents, being a derivative of nitrosourea. Diabetic nephropathy, characteristic of type 1 diabetes, is induced by injecting this substance intravenously (approaching the vein in the tail) or intraperitoneally.(14,18))	Mouse; Rat	21-35 days
Adriamycin	Adriamycin is a medicinal substance used as an antineoplastic, which can cause glomerular nephropathy and even nephrotic syndrome in the experimental animal, through the lesion produced in the podocytes. The substance is administered by intravenous injection, using the vein in the tail. This route of administration is preferred, as intraperitoneal administration may cause variations in its absorption through the peritoneal membrane.(8,12,14)	Mouse; Rat	28 days
Folic Acid	Folic acid, known as vitamin B9, can cause tubulointerstitial fibrosis using high doses, administered intraperitoneally to rodents. The induction of renal pathology has as substrate on the one hand the tubular obstruction through the crystals of folic acid, and on the other hand the direct toxic effect on the cells of the tubular epithelium.(6,19)	Mouse; Rat	21-28 days

DISCUSSIONS

Our main concern was to describe a few surgical and therapeutic methods, responsible for inducing several fibrotic processes and other processes as well, which are relevant for the onset of CKD. In the current paper we have focused on the most popular CKD induced at laboratory animals, such as nephrectomy 5/6, unilateral ureteral obstruction, some of these have been researched in a significant number of scientific papers since they can be applied on small rodents. The models described in the current paper are not perfect, but they can cause renal impairment, either by losing nephrons, or through obstruction, some by provoked ischemia or direct toxicity, especially at tubular level.

There is obviously a certain interspecificity that we have to be constantly reminded of when we apply such pathological models. An example could be the difference among the species of small rodents that we have studied in the current research, as well as the interspecific genetic variability of the gene which encodes renine. Thus, if in the case of rats there is only one copy of the gene which encodes renine, in the case of mice there are two alternative genotypes, the effect being an exacerbated plasma activity.(7) This aspect is very important since we know the major role that renine angiotensin aldosterone system plays in the renal pathology.

CONCLUSIONS

Animal models of CKD are extremely useful, but we cannot say that they perfectly reproduce human renal pathology. This is the reason why the translation of the results in clinical practice must be done with the necessary reservations, because, as it is known, the therapeutic response can be characterized by interspecific and interindividual variability. Despite these translational limitations and even if these models are not perfect, using them in experimental medicine, many pertinent conclusions can be drawn. It is important to choose a model as fit as possible on the type of renal pathology, on which we focus, so we can find similarities and differences in the mechanisms of induction, maintenance and progression, CKD in humans or even new biomarkers so useful in detecting dysfunction renal.(7,20)

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