Revista Electrónica de Biomedicina
Electronic Journal of Biomedicine

ISSN: 1697-090X

Inicio
Home

Indice del volumen
Volume index

Comité Editorial
Editorial Board

Comité Científico
Scientific Committee

Normas para los autores
Instruction to Authors

Derechos de autor
Copyright

Contacto/Contact:

AN ANIMAL MODEL FITS FOR STUDYING DIVERGENCES AMONG DIABETIC MICROVASCULAR COMPLICATIONS

Juan Carlos Picena PhD.[1] Stella Maris Daniele PhD.[2] María Cristina Tarrés PhD.[1, 3] Silvana Marisa Montenegro PhD.[1, 3] Stella Maris Martínez PhD.[1, 3] Alberto Enrique D'Ottavio PhD.[1, 3]

[1]Facultad de Ciencias Médicas
[2]Facultad de Ciencias Bioquímicas y Farmacéuticas,
[3]Consejo de Investigaciones
Universidad Nacional de Rosario. Rosario. Argentina

aedottavio @ hotmail.com

Rev Electron Biomed / Electron J Biomed 2005;2:39-43

Comment of the reviewer Erhan Suleymanoglu PhD. Department of Pharmaceutical Chemistry, Gazi University. Gazi Mahallesi, Ankara. Turkey

Comment of the reviewer Pedro Abáigar Luquín MD. PhD. Nefrología Dept. Hospital General Yagüe. Burgos, Spain

---

SUMMARY
A comparison is made between data reported by Kanauchi et al (1998) in patients with a rare occurring divergence (advanced nephropathy without retinopathy) and others, obtained in a similar line of rats (eSS), accepted as a general model for type 2 diabetes. This comparison reveals attracting analogies from different standpoints (methods employed, age, gender, lack of obesity, duration and control of diabetes, biochemical - total urinary protein excretion, serum creatinine and clearance of creatinine - and microscopic analysis). Such analogies allow proposing to eSS as an animal model for the particular study of the referred nephro- retinian divergences as well as others, opportunely reported in diabetic patients.

Keywords: Rats, biological model, diabetes, microangiopathy

RESUMEN
Se comunica una comparación hecha entre datos reportados por Kanauchi et al (1998) en pacientes con una rara divergencia (neuropatía avanzada sin retinopatía) y otros obtenidos en una línea similar

de ratas (eSS), aceptada como modelo general para el estudio de la diabetes tipo 2. Dicha comparación arroja analogía atractivas desde distintos puntos de vista (métodos empleados, edad, género, ausencia de obesidad, duración y control de la diabetes, análisis bioquímicos - excreción proteica urinaria total, creatininemia y clearance de creatinina) y microscópicos. Tales analogías permiten proponer a las ratas eSS como modelo para el estudio particular de las referidas divergencias reno-retinianas así como de otras, oportunamente comunicadas en pacientes diabéticos.

Palabras Clave: Ratas, modelos biológicos, diabetes, microangiopatía.

INTRODUCTION

Concordance is usually found between eye and kidney complications of patients with diabetes mellitus. Although some studies have shown the presence of severe retinopathy without nephropathy, overt nephropathy without retinopathy is rare. In this regard, Kanauchi et al (1998) studied 5 out of 122 patients with advanced nephropathy but without retinopathy, summarizing some clinical, therapeutic, biochemical and histological data linked to its nephropathy. The divergence between this kind of nephropathy and the concomitant lack of retinopathy led these authors to hypothesize that there could exist important differences in some aspects of the pathogenesis of nephropathy and retinopathy based upon the existence of specific organ-related pathogenic factors. Consequently, the use of animal models for deepening these aspects clearly appeared[1].

Taking into account the aforesaid considerations, the relevance of microvascular complications in diabetes and the need of spontaneous type 2 diabetic models in congruence with related WHO recommendations (Diabetes Mellitus: Report of a WHO Study Group, 1985)[2], we rescued results opportunely registered in the the non-obese IIM / Fm eSS rats, developed and raised in our laboratory (Rosario Medical School) and accepted as a model of type 2 diabetes[3-6].

Thus, the present paper deals with the analogies found between Kanauchi's report and data obtained from eSS rats, turning these animals not only a suitable model for studying type 2 diabetic microvascular complications in general but the above mentioned divergence in particular.

MATERIAL AND METHODS

Studying diachronically the onset and evolution of nephropathy in eSS rats, 20 non-obese IIM/Fm eSS (eSS) male animals were analyzed at 21 months of age. Complementarily, 14 Wistar male rats were used at the same age as non diabetic controls.

Animals were exposed to controlled temperature (21º to 25º C) and artificial light (from 0700 to 1700) until they were euthanized, receiving water and a commercial balanced diet (Cargill Co., Buenos Aires, Argentina) ad libitum.

Rats were housed in individual metabolic cages. For serum measurements, blood samples were obtained by tail vein puncture. Serum fructosamine (glycosilated protein) was analyzed through the blue nitrotetrazolium reduction method, total urinary protein excretion was determined by a quantitative method, serum creatinine was dosed by a kinetic colorimetric method and the cleareance of creatinine was calculated following the Cokcroft Gault equation [i.e: Urinary creatinine x Urinary volume. / Serum creatinine] On the other hand, rats were euthanized by ether overdose and their kidneys and eyes, excised. For anatomopathological analysis, kidneys were horizontally cut at the renal pelvis level and eyes, equatorially cut. Specimens were immediately fixed in 10 % neutral formalin, embedded in paraffin wax, sectioned at 6 um and stained with hematoxylin-eosin (HE). Some kidney sections were also stained with Periodic Acid-Schiff (PAS).

This investigation was approved by the local ethical committee, functioning according to The UFAW Handbook on the Care and Management of Laboratory Animals (2005) and FRAME's guidelines on papers involving the use of laboratory animals (1999).

RESULTS

The eSS rats revealed high serum fructosamine (eSS = 180 ± 6; Wistar =. 71 ± 7 µmol / l, p< 0.001) and showed, in relation with its diabetic nephropathy:

(1) high total urinary protein excretion (mg / 24 h) (eSS = 341 ±39 ; Wistar = 30 ±5, p<0.001);
(2) high serum creatinine (mg/dl) (eSS = 1.72 ±0.05; Wistar = 0.75 ±0.20, p<0.001) and
(3) altered glomerular filtration rate in accordance with the clearance of creatinine (ml / min) (eSS = 0.40 ±0.03; Wistar = 1.00 ±0.05, p<0.05).

From an anatomopathological standpoint, kidneys were strikingly affected in eSS rats. Glomerular involvement was noticeable consisting of diffuse hypertrophy of the mesangial tissue and thickening of the basement membrane. Tubules appeared dilated and evidenced markedly atrophic areas, with cellular vacuolation and desquamation and containing acidophilic proteinaceous material.

Finally, a complete absence of retinopathy was corroborated in eye sections.

In contrast, neither renal nor ocular lesions were detected in Wistar controls.

DISCUSSION

Kanauchi et al. (1998) communicated a rare divergent case (diabetic nephropathy without a concomitant retinopathy) in 5 male patients whose mean age was 61 ± 4 years old and whose mean duration of diabetes was 10.8 ± 2 years. Those authors reported an unsatisfactory control of the diabetes syndrome (glycosilated hemoglobin = 8 ± 1.2 %) in the studied patients, absence of retinopathy and biochemical and histopathological data revealing an advanced diabetic nephropathy. In this regard, they biochemically demonstrated high total urinary protein excretion (3920 ± 295 mg / 24 h); high serum creatinine (2.6 ± 2.07 mg/dl) and altered glomerular filtration rate in accordance with the clearance of creatinine (59 ± 13 ml / min). From an anatomopathological standpoint, Kanauchi et al. found diffuse glomerular lesions with and without nodular lesions as well as advanced arteriolar hyalinosis affecting glomerular arterioles.

Taking into account our results and although a straight comparison among data obtained from diabetic patients and rats is unviable, its paired visualization may become at least indicative when some characteristics match.

In this case, the analogies between patients and eSS rats appear conspicuous in relation with similar methods employed, comparable ages, same gender, lack of obesity, long duration of diabetes, poor or null diabetic control (unsatisfactory in patients and null in eSS rats - commercial diet ad libitum with high fructosamine-) and with biochemical and anatomopathological alterations.

Beyond the expectable differences among species, the detected analogies lead us to propose to this line, already accepted as a general model for type 2 diabetes, as a particular murine model to deepen the specific factors involved in microvascular complications of diabetes, its complex pathogenesis and the concordances and discordances of its appearances in distinct organs of human economy[7-10].

REFERENCES:

1. Kanauchi M, Kawano T, Uyama H, Shiiki H, Dohi K. Discordance between retinopathy and nephropathy in type 2 diabetes. Nephron 1998, 80: 171-174

2. World Health Organization. Diabetes Mellitus: Report of a WHO Study Group. Geneva, World Health Org. (Tech. Rep. Ser., no. 727), 1985

3. Tarrés MC, Martínez SM, Montenegro SM, Llorens A, Picena JC, Naves A. Am. J. Pathol. 1992, 141: 761- 763

4. Martínez SM, Tarrés MC, Montenegro SM, Milo R, Picena JC, Figueroa N. Rabasa S. Acta Diabetol. Lat. 1998, 25: 303-313

5. Martínez SM, Tarrés MC, Montenegro SM, Revelant G, Figueroa N, Alonso D, Laudanno OM., D'Ottavio AE. Acta Diabetol Lat.1990, 27: 329-336

6. Martínez SM, Tarrés MC, Picena JC, Montenegro SM, Gagliardino JJ, Gómez-Dumm, CLA, D'Ottavio AE, Naves A, Rabasa SL In Lessons from animal diabetes IV. Smith-Gordon, London 1993, pp. 75-90

7. Phillips A, Janssen U, Floege J. Progression of diabetic nephropathy. Insights from cell culture and animal models. Kidney Blood Press Res. 1999, 22: 81-97

8. Dalla Vestra M, Saller A, Mauer M, Fioretto P. Role of mesangial expansion in the pathogenesis of diabetic nephropathy. J Nephrol. 2001,14 (Suppl 4): S51-57

9. Wolf G, Ritz E. Diabetic Nephropathy in Type 2 Diabetes Prevention and Patient Management J Am Soc Nephrol. 2003, 14:1396-1405

10. Sone H, Mizuno S, Yamada N: Vascular risk factors and diabetic neuropathy. N Engl J Med.2005, 352: 341-350

This paper was supported by grants of the National University of Rosario

Corresponding author
Alberto Enrique D'Ottavio -Matheu 371
2000 Rosario, Argentina
Teléfono 54 0341 4556101-
E-mail: aedottavio @ hotmail.com

Comment of the reviewer Erhan Suleymanoglu PhD. Department of Pharmaceutical Chemistry, Gazi University. Gazi Mahallesi, Ankara. Turkey

This research report focuses on the relevant use of eSS rats as animal model for following the onset and evolution of diabetes, with particular emphasis on divergences occuring in diabetic patients. For comparisons with previous data for patients with advanced nephropathy without retinopathy, as well as other parameters, obtained with a generally accepted murine model for type 2 diabetes-eSS line rats, the authors emphasized the importance of the use of suitable animal models for deducing certain interrelationships between eye and kidney complications and specific organ-related pathogenic factors. To find link between previously described patients results and those obtained for eSS rats, as a promissing animal model, in terms of explaining those divergences, non-obese IIM/Fm eSS line was compared to Wistar male rats as negative controls, respectively.

Biochemical analysis showed increased levels of serum parameters, while pathoanatomic examination depicted lack of retinopathy in eye sections of rats. In accordance with conspicuous analysis between patients and eSS rats, the observed matching values has led the authors to suggest eSS rats as a useful murine model for following divergences among diabetic microvascular complications.

This interesting contribution of colleagues from Rosario Medical School of The National University of Rosario, in Rosario, Argentina is a valuable contribution to the current understanding of employment of animal models for studying organ-specific pathogenesis of diabetes.

Comment of the reviewer Pedro Abáigar Luquín MD. PhD. Nefrología Dept. Hospital General Yagüe. Burgos, Spain
The authors show us an interesting animal model to explore not only the relationship between diabetes and nephropathy, but a rare association betwwen diabetes and nephropathy without retinopathy.

This last syndrome was not usual in clinical practice and because of the heterogenicity of human patients it could be interesting to try to find an animal model-like the author's rats- where these possibilities might be explored.

Besides, in spite the jump between species, this model would lead us a way to open the door of the complex pathogenesis of microvascular complications of diabetes.

Received July 5, 2005
Published July 23, 2005