Kidney International, Vol 53 (1998), pp. 508–509

EDITORIAL

Apolipoprotein AI and amyloidosis: A genetic model for aging

Less than ten years have passed since apolipoprotein AI (ApoAI) joined the ranks of acknowledged amyloid forming proteins [1, 2]. Certainly ApoAI has had a long history in medical science attesting its central role in normal lipid metabolism and metabolic perturbations that lead to prominent diseases such as atherosclerosis. The discovery that a variant form of ApoAI could form amyloid fibrils and cause a unique type of protein deposition disease opened an entirely new career for this protein, which was always assigned the role of a facilitator but never that of the lead actor in a disease. This is the unique feature of the amyloid diseases. The protein defines the disease, and it is the protein, we believe, that is central to the process that leads to fibrillogenesis, fibril deposition, organ dysfunction, and finally death.

The evolution of knowledge of ApoAI in this area has been very interesting and thought provoking. Five mutations in the ApoAI gene have now been found to result in autosomal dominant amyloidosis. Three of these are the result of single nucleotide changes giving amino acid substitutions in the amino terminal portion of the protein [3–6]. Two, as exemplified by the article by Persey et al, in this issue of the journal, are the result of deletions in the gene for AI [7, 8]. In most cases the mutations lead to nephropathic amyloidosis with varying degrees of hepatic, splenic, and neural pathology.

ApoAI is not the sole cause of hereditary renal amyloidosis. It shares this distinction with fibrinogen Aα-chain, lysozyme, and in some families, transthyretin, cystatin c, and gelsolin [9]. Indeed, ApoAI is not the only apolipoprotein associated with amyloidosis. Serum amyloid A (SAA) in most mammalian species and ApoAII in mice are also amyloid forming apolipoproteins. ApoAI does, however, offer interesting parallels to other diseases and raises questions about normal physiology.

It is now known that the pulmonary amyloid deposits in aging dogs are formed from ApoAI [10], and amyloid deposits in the aortae of aged humans is a product of ApoAI [11]. In both cases the fibrils appear to be synthesized from the normal protein. The same phenomenon appears to be true with transthyretin, which can give senile cardiac amyloidosis without the presence of a mutated form of the protein. Also, it has been recognized for many years that amyloid deposits found in aging members of many mammalian species is formed from normal SAA, and of course, most cases of Alzheimer disease are associated with amyloid plaques formed from normal amyloid β-peptide. These examples all support the hypothesis that certain normal proteins are destined to form amyloid with time, and mutations in these proteins only accelerate the process. The implication for a species which increasingly is of the mind set that life expectency should continue to increase indefinately is daunting.

The association of amyloid with aging is becoming an increasingly important subject for scientific investigation. Areas of research that have not been explored in detail include age-associated protein repair mechanisms and age associated changes in the catabolism of proteins. One plausible basis for amyloid formation from a physiologically normal protein is that time dependent post-translational changes in the protein are not metabolically corrected and resultant structure changes lead to fibrillogenesis. Another possibility is that catabolic mechanisms change with age and these lead to persistence of incompletely proteolyzed peptides that have an innate propensity for fibril formation. Support for the latter possibility is the finding of increased plasma turnover of the Gly26Arg variant of ApoAI, which is associated with amyloidosis [12]. Also, metabolic differences between normal and amyloid associated variants of transthyretin support the hypothesis that catabolism of these proteins is important to amyloid pathogenesis [13]. If we can define these changes in metabolism of amyloid forming proteins, we may start to understand the basis of aging.

MERRILL D. BENSON
Indianapolis, Indiana, USA

Reprint requests to Merrill D. Benson, M.D. Department of Medical and Molecular Genetics, Indiana School of Medicine, Medical Research and Library Building 130, 975 West Walnut St., Indianapolis, Indiana 46202-5251, USA.

REFERENCES

1. NICHOLS WC, DWULET FE, LIEPNIEKS J, BENSON MD: Variant apolipoprotein AI as a major constituent of a human hereditary amyloid. *Biochem Biophys Res Commun* 156:762–768, 1988
2. NICHOLS WC, GREGG RE, BREWER HB, BENSON MD: A mutation in apolipoprotein A-I in the Iowa type of familial amyloidotic polyneuropathy. *Genomics* 8:318–323, 1990
3. JONES LA, HARDING JA, COHEN AS, SKINNER M: New USA family has apolipoprotein AI (Arg26) variant, in *Amyloid and Amyloidosis 1990*, VIth International Symposium on Amyloidosis, August 5–8, 1990, Oslo, edited by NATVIG JB, FORRE O, HUSBY G, HUSEBEKK A, SKØGEN B, SLETTEN K, WESTERMARK P, DORDRECHT/BOSTON/LONDON, KLUWER ACADEMIC PUBLISHERS, pp 385–388
4. VIGUSHIN DM, GOUGH J, ALLAN D, ALGUACIL A, PENNER B, PETTIGREW NM, QUINONEZ G, BERNSTEIN K, BOOTH SE, BOOTH DR, SOUTAR AK, HAWKINS PN, PEPYS MB: Familial nephropathic systemic amyloidosis caused by apolipoprotein AI variant Arg 26. *Q J Med* 87:149–154, 1994
5. BOOTH DR, TAN SY, BOOTH SE, HSUAN JJ, TOTTY NF, NGUYEN O, HUTTON T, VIGUSHIN DM, TENNENT GA, HUTCHINSON WL, THOMSON N, SOUTAR AK, HAWKINS PN, PEPYS MB: A new apolipoprotein AI variant, Trp50Arg, causes hereditary amyloidosis. *Q J Med* 88:695–702, 1995
6. SOUTAR AK, HAWKINS PN, VIGUSHIN DM, TENNENT GA, BOOTH SE, HUTTON T, NGUYEN O, TOTTY NF, FEEST TG, HSUAN JJ, PEPYS MB: Apolipoprotein AI mutation Arg60 causes autosomal dominant amyloidosis. *Proc Natl Acad Sci USA* 89:7389–7393, 1992

Key words: fibrillogenesis, protein mutation, aging, genetics

Received for publication October 21, 1997
Accepted for publication October 21, 1997

7. Booth DR, Tan SY, Booth SE, Tennent GA, Hutchinson WL, Hsuan JJ, Totty NF, Truong O, Soutar AK, Hawkins PN, Bruguera M, Caballeria J, Solé M, Campistol JM, Pepys MB: Hereditary hepatic and systemic amyloidosis caused by a new deletion/insertion mutation in the apolipoprotein AI gene. *J Clin Invest* 97:2714–2721, 1996
8. Persey MR, Booth DR, Booth SE, van Zyl-Smit R, Adams BK, Fattaar AB, Tennent GA, Hawkins PN, Pepys MB: Hereditary nephropathic systemic amyloidosis caused by a novel variant apolipoprotein AI. *Kidney Int* 53:276–281, 1998
9. Benson MD: Amyloidosis, in *The Metabolic and Molecular Bases of Inherited Disease* (7th ed, vol III, chap 139, part 18 *Connective Tissues*), edited by Scriver CR, Beaudet AL, Sly WS, Valle D, New York, McGraw Hill Book Co., 1995, pp 4159–4191
10. Johnson KH, Sletten K, Hayden DW, O'Brien TD, Roertgen KE, Westermark P: Pulmonary vascular amyloidosis in aged dogs. A new form of spontaneously occurring amyloidosis derived from apolipoprotein AI. *Am J Pathol* 141:1013–1019, 1992
11. Westermark P, Mucchiano G, Marthin T, Johnson KH, Sletten K: Apolipoprotein AI-derived amyloid in human aortic atherosclerotic plaques. *Am J Pathol* 147:1186–1192, 1995
12. Rader DJ, Gregg RE, Meng MS, Schaefer JR, Kindt MR, Zech LA, Benson MD, Brewer HB Jr: *In vivo* metabolism of a mutant apolipoprotein, apoA-I_{Iowa}, associated with hypoalphalipoproteinemia and hereditary systemic amyloidosis. *J Lipid Res* 33:755–763, 1992
13. Hanes D, Zech L, Murrell JR, Benson MD: Metabolism of Normal and Met30 Transthyretin, in *Advances in Food and Nutrition Research* (Chapter 8, Metabolism of Transthyretin, Vol 40) 1996, pp 149–155