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Personal View

Lipids and the eye

Sheila M. Crispin *,[1]

Cold Harbour Farm, Underbarrow, Kendal, Cumbria LA8 8HD, UK

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Background

In June 2015, I was delighted and honoured to receive the Kennel Club Charitable Trust's Lifetime Achievement Award for research in the field of canine health, sponsored by Vernon and Shirley Hill of Metro Bank, and administered by the Kennel Club Charitable Trust. As with many veterinary clinicians, my research has involved diverse subjects in veterinary science, not all of which have involved ocular disease. However, hyperlipoproteinaemia and ocular lipid influx and clearance have provided a fascinating area for study and are the subject of this personal view.

I was exceedingly fortunate to encounter Dr Keith Barnett early in my veterinary training; Keith was Head of the Unit of Comparative Ophthalmology at the University of Cambridge, a veterinary ophthalmologist with an international reputation, who attracted fellow enthusiasts from all over the world. He enlivened the preclinical anatomy course with a fascinating account of comparative ophthalmology and I was hooked. It was Keith who suggested that some of the corneal opacities affecting dogs might provide interesting avenues for research.

Introduction

Many years ago, it was shown that the rather strange corneal opacities, now classified as Schnyder Corneal Dystrophy in humans, were composed of lipids and subsequent studies into the pathogenesis of ocular lipid deposition were stimulated in a variety of species (herbivores, carnivores and omnivores). These studies followed two lines of research, brought together in a major review published in *Progress in Retinal and Eye Research* in 2002 (Crispin, 2002). The first pursued the systemic factors, which are of importance in ocular lipid deposition; the second pursued the local ocular factors which might be involved. This personal view will be based on my research in the dog, with examples from other species included, as a comparative approach helps our understanding of the underlying pathogenesis.

Systemic factors and ocular lipid influx

The systemic factors that are involved in ocular lipid influx can be summarised in terms of species, breed, genotype, age and sex, all of which are non-modifiable factors. The major modifiable systemic factors include disease, diet and exercise. When I started my research in 1973, there were few published studies in animals other than experimental animals such as rabbits and dogs and these studies were not necessarily comparable with the pet population seen in clinical practice; indeed some of the experimental systems were unhelpful as putative models of animal or human disease. My initial studies had indicated breed susceptibility to different types of lipid deposition, but also showed that susceptibility was by no means linked with the plasma lipid and lipoprotein profile (Crispin, 1984). Our research group studied the effect of breed, oestrus, diet and exercise in dogs on the lipoprotein profile (Bolton et al., 1990; Crispin et al., 1992; Downs et al., 1993, 1994, 1997a, 1997b; Downs, 1995) as well as extending studies on the complexities of lipid influx and efflux, associated with clinical conditions in a variety of veterinary species (Crispin et al., 1988; Crispin, 2002).

To understand the pathogenesis of lipid deposition in different tissues, it is important to understand some of the key biochemical differences between species. Although albumin acts as a binding protein for the transport of free fatty acids (FFAs) in plasma, most plasma lipids are packaged as lipoproteins, so that they can be transported around the body in a water-soluble form. Lipoproteins consist

* Tel.: +44 015395 68637.
E-mail address: s.m.crispin@bris.ac.uk.
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of a hydrophobic, non-polar core of cholesteryl esters and triglycerides (synonym: triacylglycerides), surrounded by a membrane-like shell of free cholesterol, phospholipids and protein; the latter termed apoprotein or apolipoprotein and usually abbreviated to 'apo'.

It is the apoproteins that determine lipoprotein structure and function, but historically the nomenclature has been based on the lipoproteins. Empirical classification of lipoproteins is usually based on physical properties such as composition, size, density and charge, but it is important to emphasise the highly labile nature of the system, implicit in the term lipoprotein cascade.

The relative size and density of lipoproteins vary according to the proportion of lipid to protein and the largest lipoproteins are the least dense, due to their high lipid content. The main lipoprotein classes are chylomicrons (CM), the largest and least dense, followed by very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high density lipoproteins (HDL), the latter being smallest and densest.

The lipoproteins can be categorised according to their principal metabolic functions. The role of chylomicrons and VLDL is to transport triglycerides, as a source of fatty acids, from the intestine or liver to the peripheral tissues. LDL primarily delivers cholesterol to tissues, via the classical receptor mediated cellular uptake pathway described by Goldstein and Brown (1977). HDL, aided by the enzyme lecithin–cholesterol acyltransferase (LCAT), is involved in transporting excess cellular cholesterol back to the liver for excretion in the form of bile acids. The classical HDL scavenging process is known as reverse cholesterol transport, but there is also a non-biliary reverse cholesterol transport route for faecal cholesterol excretion in both humans and dogs, known as the transintestinal cholesterol efflux pathway and the contribution of this pathway has not been fully determined in either species.

There has been increasing recognition that some species are more susceptible to atherogenesis than others and there is now a greater understanding of the underlying biology. Athero-susceptible mammals include humans and rabbits and athero-resistant mammals include cats and dogs. There are notable differences in lipid metabolism between these two groups. In humans and rabbits, LDL is the major cholesterol carrier, whereas in dogs and cats, HDL plays this role.

Plasma cholesteryl ester transfer protein (CETP), which facilitates the transfer of cholesteryl ester (CE) from high density lipoprotein (HDL) to VLDL and LDL, is highly active in humans and rabbits, but not in cats and dogs, where the activity of CETP may be undetectable (Ha and Barter, 1982). In humans, two thirds of classical reverse cholesterol transport is via the indirect pathway utilising VLDL and LDL.

Phospholipid transfer protein (PLTP) is involved in phospholipid transfer from triglyceride-rich lipoproteins and modulates HDL size and composition (Albers et al., 2012), with athero-resistant species having the highest level of activity. CETP and PLTP contribute to the classical reverse cholesterol transport pathway by modifying HDL metabolism and cellular cholesterol efflux.

Human and feline HDL can be subdivided into HDL_2 and HDL_3. These particular HDL acquire cholesteryl esters through the action of lecithin–cholesterol acyl transferase (LCAT), which circulates in the blood bound to HDL and is involved in converting free cholesterol to CE. In dogs, however, HDL_2 molecules continue to acquire CE through the action of LCAT, leading to the formation of HDL_1 molecules, which are unique to the dog (Mahley et al., 1974). HDL_1 is removed from the circulation by the liver, via the binding of apoE to the hepatocyte receptor.

These mechanisms and the species differences highlighted are fundamental to understanding why dogs and cats are resistant to spontaneous atherosclerosis and are also of relevance when comparing the ocular manifestations of hyperlipoproteinaemia in dogs and cats with those of humans and rabbits.

Primary and secondary hyperlipoproteinaemia in the dog and cat

Postprandial lipaemia, characterised by a rise in triglyceride-rich lipoproteins, is a normal phenomenon that follows ingestion of food. Humans on a typical Western diet spend around 18 out of 24 h in this state (Sharrett et al., 2001), whereas this is not the case in dogs fed once daily, where baseline values are usually restored after no more than 8 h (Downs et al., 1997b).

Chylomicrons should be absent from a normal fasting plasma sample, as their half-life is relatively short, although chylomicron clearance is slower on high fat diets. A number of primary chylomicronaemia syndromes are recognised as inherited conditions in humans (Crispin, 2002). Similarly, a familial lipoprotein lipase deficiency, inherited as an autosomal recessive trait (Jones et al., 1983) and caused by a mutation in the lipoprotein lipase gene, has been recognised as the underlying cause of primary chylomicronaemia in cats (Ginzinger et al., 1996). Severe fasting hypertriglyceridaemia (5 to 126 mmol/L) and anaemia (packed cell volume <11%) have also been reported in kittens around the time of weaning (Gunn-Moore et al., 1997) and although lipoprotein lipase activity was low in the affected kittens, unaffected siblings and their parents, none had the LPL gene mutation reported by Ginzinger et al. (1996). Primary chylomicronaemia can also occur in the dog, particularly the Miniature Schnauzer breed, and increased plasma triglycerides appear to predispose affected dogs to developing pancreatitis. Secondary chylomicronaemia is most commonly associated with diabetes mellitus in dogs, cats and humans.

A number of familial hypertriglyceridaemias are recognised in humans (Crispin, 2002) and there is possibly a genetically determined disorder in the Burmese breed of cat, a breed which is also at increased risk of obesity (Lee et al., 2013) and diabetes mellitus (Öhlund et al., 2015), where dysregulation of lipid metabolism, particularly in relation to triglycerides, has been proposed as the underlying defect. Secondary hypertriglyceridaemia is common in dogs, cats and humans with diabetes mellitus.

Primary hypercholesterolaemia in humans is caused by excess LDL, although some familial forms of hypercholesterolaemia involve both LDL and VLDL (Crispin, 2002). Secondary causes of hypercholesterolaemia in dogs and humans usually have an identifiable metabolic cause, such as hypothyroidism, hyperadrenocorticism, cholestatic liver disease or the nephrotic syndrome (Crispin, 2002; Johnson, 2005). While raised LDL and VLDL are typical of combined hyperlipidaemia in humans, in dogs it is not unusual for HDL, LDL and VLDL to be raised in established metabolic diseases such as hypothyroidism and hyperadrenocorticism.

There are more subtle variations of the canine lipoprotein profile associated with raised circulating cholesterol, such as a higher level of HDL cholesterol, which might be genetically determined and could render some breeds, such as the Golden retriever, more susceptible to the type of corneal lipid deposition that characterises lipid keratopathy (Bolton et al., 1990; Crispin, 2002). Corneal lipid deposition, on occasions associated with hypercholesterolaemia, has been identified in other breeds in the United Kingdom, including the Afghan hound, Cavalier King Charles spaniel, German shepherd dog, Shetland sheepdog and Rough collie (Crispin and Barnett, 1983). No primary genetic defect has yet been determined in any of these breeds, although research involving Cavalier King Charles spaniels has indicated that a defect of corneal keratocyte metabolism may be the underlying defect in the corneal lipid deposition, termed Crystalline Corneal Dystrophy, or Crystalline Stromal Dystrophy (Crispin, 1988), which resembles human Schnyder Corneal Dystrophy to the extent that it might tentatively be described as Schnyder-like Corneal Dystrophy. The ocular manifestations in the Cavalier King Charles spaniel may be modified by raised circulating lipoproteins, as is the situation in the similar human disorder.