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Review

Comparative aspects of blood coagulation

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Abstract

Blood coagulation is a basic physiological defense mechanism that occurs in all vertebrates to prevent blood loss following vascular injury. In all species the basic mechanism of clot formation is similar; when endothelium is damaged a complex sequence of enzymatic reactions occurs that is localized to the site of trauma and involves both activated cells and plasma proteins. The reaction sequence is initiated by the expression of tissue factor on the surface of activated cells and results in the generation of thrombin, the most important enzyme in blood clot formation. Thrombin converts soluble fibrinogen, via soluble fibrin monomers, into the insoluble fibrin that forms the matrix of a blood clot as well as exerting positive-feedback regulation that effectively promotes additional thrombin generation that facilitates the rapid development of a thrombus. Both spontaneous and trauma-induced haemorrhagic episodes can develop in all mammals with inherited or acquired abnormalities in one or more of the coagulant proteins.

Experimental studies with plasma from a wide range of species have led to the conclusion that there are extensive differences in the rates of thrombin generation and fibrin formation among species. However, current evidence suggests that at least some of these quantitative differences are likely due to the use of non-species specific laboratory reagents. Although the individual proteins involved in the procoagulant pathways exhibit similar functions in all animals, differences in amino acid sequence cause incomplete homology and varying degrees of immunological cross-reactivity for the same protein across species.

Keywords: Blood coagulation; Vertebrates; Haemostasis; Thrombosis

1. Introduction

Haemostasis is a fundamental defense mechanism of all vertebrates and involves two complementary processes: the formation of a blood clot, or thrombus, to stem blood loss from a damaged vessel and the process of thrombus dissolution, or fibrinolysis, once endothelial repair has occurred. These are complex processes involving multiple interdependent interactions among platelets, endothelial cells, white cells and plasma proteins. By convention, many of the procoagulant plasma proteins are referred to as Factors with assigned Roman numeral designations. The proteases involved in clot formation circulate in their inactive, or zymogen, forms that, in healthy animals, only become biologically active when the vasculature is perturbed.

In part because of the limited availability of reliable laboratory assays for use with plasma from non-human vertebrates, comparative aspects of the fibrin clot formation processes are better understood than are those of fibrin clot dissolution or fibrinolysis. Thrombin is the most important enzyme in the haemostatic process and is produced "on demand" from its circulating precursor, prothrombin, in response to any type of haemostatic activator. The sequential and co-ordinated interactions of the procoagulant proteins that initiate and amplify thrombin formation (Fig. 1) are offset by a group of circulating anticoagulant, or inhibitory, proteins that function to ensure that thrombin generation is confined to the area of vascular trauma and that excess thrombin is not generated (Gentry and Downie, 1993). There is

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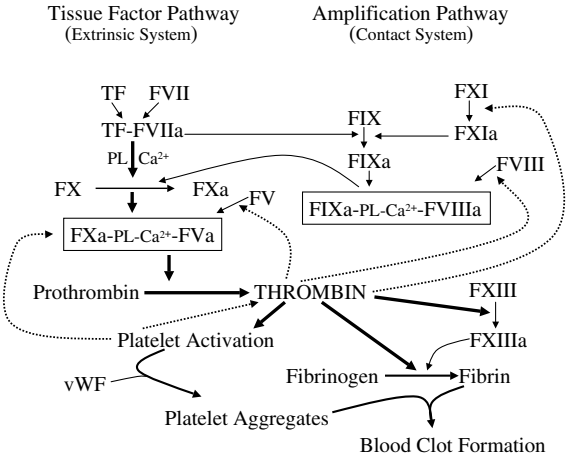

Fig. 1. Schematic diagram of the coagulation cascade. The initiation of blood clot formation occurs following vascular injury and the exposure of tissue factor (TF) to circulating blood. Thrombin exerts positive feedback regulation (dotted lines) by activating platelets and other procoagulant proteins. Activated platelets provide a phospholipid (PL) surface that serves to enhance enzyme complex formation. Platelet aggregates are anchored to damaged endothelium by von Willebrand Factor (vWF). The majority of proteins are designated as factors (F) and Roman numerals.

limited information about the anticoagulant proteins in non-human plasma (Johnstone, 2000). Hence, this review focuses on comparative aspects of the interaction of the procoagulant proteins and fibrin formation in vertebrates.

2. Evolution of blood clotting in vertebrates

In both anthropods and vertebrates, blood clot formation occurs following trauma to a vessel wall that, in turn, initiates a cascade of enzymatic reactions culminating in the conversion of a soluble protein into an insoluble polymer (Iwanaga, 1993; Theopold et al., 2002). In the horseshoe crab (*Limulus* spp.), activation of the clotting system causes the release of procoagulant proteins from haemocytes (Iwanaga et al., 1992). This response is analogous to the role of vertebrate platelets in clot formation. In lobsters, crabs and crayfish, the final reaction in the haemostatic process is the conversion of a vitellogenin-like protein to its insoluble form by a transglutaminase enzyme (Iwanaga, 1993; Hall et al., 1999). This reaction is similar to the thrombin-activated transglutaminase (Factor XIII) modification of soluble fibrin to insoluble fibrin in vertebrates (Spurling, 1981; Aeschlimann and Paulsson, 1994). In a comparative study, similar levels of Factor XIII were observed in plasma from 15 species including poultry, laboratory and domestic animals, although immunological differences were noted, especially between the avian and mammalian forms of the protein (Lopaciuk et al., 1978). In contrast, among all species there is considerable structural similarity in the fibrinogen molecule (Doolittle, 1984).

It has been postulated that procoagulant proteins have evolved in vertebrates through the classical route of gene duplications, point mutations and divergence of function from ancestral proteins that are part of the general defense system that protects against infection and injury (Patthy, 1990). Based on the isolation and characterization of cDNAs from chickens and puffer fish (*Fugu rubripes*) with sequence identity to Factor V (FV), Factor VII (FVII), Factor VIII (FVIII), Factor IX (FIX) and Factor X (FX), and the occurrence of these proteins along with prothrombin in the blood of zebrafish, it has been suggested that these haemostatic proteins are present in all jawed vertebrates (Jagadeeswaran and Sheehan, 1999; Davidson et al., 2003). The blood coagulation enzymes, namely prothrombin, FVII, FIX and FX are each closely related to haptoglobin and the complement proteases, C1r and C1s (Patthy, 1990). Similarly, FV and FVIII, the protein cofactors involved in thrombin generation (Fig. 1), are structurally related to ceruloplasmin, a copper-carrying acute phase protein that may also have anticoagulant properties (Church et al., 1984; Walker and Fay, 1990; Gentry, 1999). Tissue Factor (TF), the protein now recognized to be the primary stimulant to thrombin generation and, hence, to fibrin formation, is a member of the transmembrane cytokine family (Nemerson, 1988; Camerer et al., 1996; Morrissey, 2001). In contrast, Factor XI (FXI), like the other components of the "contact system", namely Factor XII (FXII), prekallikrein (PK) and high molecular weight kininogen (HK), appears to be derived from different ancestral proteins that are related to digestive enzymes (Patthy, 1990). Considering the differences in digestive physiology among vertebrates it is perhaps not surprising that, of all the haemostatic proteins, this group of proteins shows the most variation amongst species.

3. The blood coagulation cascade: current concepts

In the classical model of fibrin formation two interrelated pathways of thrombin generation and hence fibrin formation were proposed. In the 1960s, the Contact Activation, or Intrinsic, pathway was considered to be the primary pathway that triggered thrombin formation following trauma to the vascular endothelium while the Extrinsic pathway was thought to be a complementary pathway by which thrombin could be formed (MacFarlane, 1964; Davie and Ratnoff, 1964). As the role of the various proteins involved in the coagulation cascade has been elucidated, these models of thrombin generation and fibrin formation have been revised. In the current model only a single pathway, the Tissue Factor

pathway, formerly known as the Extrinsic pathway, is considered to be involved in the initiation of thrombin formation (Davie et al., 1991; Nemerson, 1992; Mann et al., 1992; Zwaal et al., 1998; Gailani, 2000; Dahlback, 2000). The Intrinsic pathway is now variously referred to as the Amplification, or Propagating pathway. A simplified schematic model of the current concept of thrombin generation and fibrin clot formation is shown in Fig. 1. One of the attractions of the revised model is that, unlike the two pathway scheme, it is relevant for all classes of vertebrates.

3.1. Initiation and propagation of thrombin formation

Tissue factor (TF) is a lipid-dependent transmembrane glycoprotein that is sequestered in the circulation in quiescent endothelial cells and monocytes. Following cellular activation by vascular trauma or an inflammatory stimulus, TF becomes exposed on the plasma membrane where it interacts with circulating FVII, or its activated form, FVIIa, to form the enzymatically reactive TF–FVIIa complex (Fig. 1). This complex functions primarily to convert FX to its activated form, FXa, but it also activates circulating FIX to FIXa (Gailani and Broze, 1991; Mann et al., 1998; Bajaj and Joist, 1999; Dahlback, 2000). FXa and FIXa can either remain associated with TF-bearing cells or they can diffuse into the blood and bind to negatively charged phospholipids (PL) exposed on the surface of activated endothelial cells or nearby activated platelets that have been attracted to the site of vascular damage (Monroe et al., 2002). The generation of thrombin requires the formation of the "prothrombinase complex" that consists of FXa, phospholipid, calcium and a protein co-factor, FV. The first few molecules of thrombin generated by this "prothrombinase complex" initiate several positive-feedback reactions that sustain its own formation and facilitate the rapid growth of the blood clot or thrombus around the area of vascular damage. For example, thrombin can convert FXI to its proteolytically active form, FXIa, that, in turn, converts FIX to FIXa (Minnema et al., 1999). FVIII normally circulates in a complex with von Willebrand factor (vWF) which effectively extends the plasma half-life of FVIII because it is protected from proteolytic degradation in the complex form. Thrombin not only dissociates FVIII from vWF but it also converts it to a more potent co-factor, FVIIIa. Both of these reactions facilitate the formation of the highly reactive "tenase complex" that consists of FIXa, FVIIIa, calcium and phospholipid. This "tenase complex" cleaves FX at the same reactive site as that cleaved by the TF–FVIIa complex and hence produces the same FXa product (Furie and Furie, 2000). The thrombin-induced conversion of FV to FVa, along with the increased availability of FXa, enhances the rate and extent of thrombin formation by the "prothrombinase" complex. Another positive feed-back response is the increased availability of phospholipids on the surface on thrombin-activated platelets that accumulate at sites of vascular damage (Gentry, 2000).

The formation of a blood clot that is impermeable to blood flow occurs once an insoluble fibrin meshwork forms around platelet aggregates. Thrombin first cleaves two peptides, fibrinopeptides A and B, from fibrinogen which alters the surface charge of the molecule and allows a covalently linked network of fibrin monomers to develop. These fibrin monomers are converted to insoluble fibrin polymers by the action of thrombin-activated Factor XIII (FXIIIa) that forms cross-links of stable peptide bonds between and within the fibrin strands to generate the insoluble fibrin polymers that form the backbone of a thrombus or blood clot (Gentry and Downie, 1993; Bick and Murano, 1994).

3.2. The revised coagulation cascade and inherited haemorrhagic disorders

FVII deficiency in beagles was one of the first inherited canine coagulation defects to be described (Poller et al., 1971; Spurling et al., 1972). FVII-homozygous deficient dogs, unlike dogs with an inherited defect of either FVIII or FIX, are usually clinically asymptomatic (Dodds, 1974; Fogh and Fogh, 1988). This differential haemorrhagic tendency in dogs with different coagulation factor deficiencies is similar to that observed in people. Inherited deficiencies of FVIII (Haemophilia A) and of FIX (Haemophilia B) have been identified in many breeds of dogs and less frequently in cats, horses and cattle (Fogh and Fogh, 1988; Dodds, 1997). Severely affected animals with $<2\%$ of normal circulating activity of either FVIII or FIX usually exhibit spontaneous haemorrhagic episodes while animals with 5+% of normal activity exhibit a broader range of symptoms from bleeding only in response to various types of stress, such as strenuous exercise, surgery and trauma, to severe spontaneous haemorrhaging. The severity of clinical symptoms in animals with deficiencies in either FVIII or FIX compared to those in animals with FVII deficiency was one of the reasons why the pathway that included FVIII and FIX was assigned the primary role in the original cascade, or waterfall, hypothesis of coagulation and only a secondary role was assigned to the pathway that included FVII (MacFarlane, 1964; Davie and Ratnoff, 1964).

In recent years considerable progress has been made in understanding the physiological roles of individual haemostatic proteins, especially from studies in which specific gene targeting in mouse embryonic stem cells creates a "knock-out" mouse that fails to express a specific coagulation factor (Carmeliet and Collen, 1996; Degen, 2001). These studies have shown that a gene deletion for TF (Bugge et al., 1996), FVII (Rosen et al.,

1997), FX (Dewerchin et al., 2000), FV (Cui et al., 1996) or prothrombin (Sun et al., 1998; Xue et al., 1998) results in fatal neonatal haemorrhaging and hence is incompatible with survival to adulthood. Consequently, animals that are homozygous deficient in any on these proteins would not be expected to survive. Indeed, no inherited defects associated with the absence of either prothrombin or FV have been reported in domestic animals. Homozygous FX-deficient dogs with less than 10% of normal plasma FX activity are frequently stillborn or die as neonates from internal bleeding. Heterozygous animals that have plasma FX activity above 30% of normal values are generally asymptomatic (Dodds, 1973; Cook et al., 1993). In contrast, FVII deficiency appears to be generally asymptomatic in both the homozygous and heterozygous condition. The plasma FVII activity in a mixed breed dog who exhibited abnormal bleeding following routine orchectomy was determined to be 0.4% of normal (Macpherson et al., 1999). This amount of FVII is apparently sufficient to trigger thrombin generation when necessary because the owners have not reported any spontaneous haemorrhages in the dog in the five years since it was first diagnosed. Studies with transgenic mice indicate that, like FVII, only trace amounts of TF are required to initiate thrombin formation. Manipulation of the TF gene to produce approximately 1% of normal TF levels was sufficient to restore normal development and haemostasis in homozygous $TF^{-}/^{-}$ mice (Graham et al., 1998).

In contrast to the effect of gene deletions involving individual components of the Tissue Factor Pathway, gene disruption of either the FVIII (Bi et al., 1996), FIX (Lin et al., 1997; Wang et al., 1997), vWF (Denis et al., 1998) or FXI (Gailani et al., 1997) gene is compatible with survival to sexual maturity in mice. However, as occurs in domestic animals and people with inherited defects in the synthesis of each of these haemostatic proteins, both spontaneous and trauma-induced haemorrhagic episodes of varying degrees of severity occur in the transgenic mice (Degen, 2001).

While TF expression and the formation of FXa by the TF–FVIIa complex (Fig. 1) is effective at initiating thrombin formation, this pathway cannot sustain thrombin generation for an extended period of time because of the presence of an anticoagulant known as tissue factor pathway inhibitor (TFPI). This protein circulates in blood bound to lipoproteins and platelets which release their TFPI after thrombin stimulation (Novotny et al., 1998). The primary function of TFPI is to inhibit the activation of FXa by TF–FVIIa (Broze, 1995). Studies with $TFPI^{-}/^{-}$ mice have provided evidence for the potential importance of TFPI in preventing thrombophilia due to unregulated thrombin formation. TFPI gene disruption causes intrauterine intravascular thrombi, consumptive coagulopathies and lethal haemorrhages in mouse embryos (Huang et al., 1997). Although plasma TFPI does not appear to have been evaluated in plasma from many domestic animals, it has been measured in bovine plasma (Roach et al., 2002).

An inherited deficiency of vWF in animals was first identified in swine in 1941 and, because of the similarities in the human and porcine forms of the disorder, not only is porcine vWF the oldest known model of a human bleeding diathesis but the pig has become one of the most widely used models for human coagulation research (Hogan et al., 1941; Fass et al., 1976; Denis and Wagner, 1999; Munster et al., 2002). vWF deficiency is the most common inherited bleeding disorder in dogs having been identified in over 50 breeds (Thomas, 1996; Brooks, 2000). When the vasculature is damaged vWF, released from storage in Weibel–Palade bodies in endothelial cells, augments plasma vWF and initially allows unactivated platelets to adhere around the area of trauma. After platelets have been activated vWF, along with fibrinogen, mediates platelet–platelet interactions that permit the anchoring and stabilization of the clot, or thrombus (Fig. 1). The role of vWF is particularly important at the high shear rate conditions encountered in arterioles and the microcirculation (Baumgartner et al., 1980). In all species, quantitative and/or qualitative abnormalities of vWF are characterized by haemorrhaging from mucosal surfaces and or excessive bleeding after surgery or trauma.

In dogs, as in people, vWF disease is classified in one of the three major categories depending on the size distribution and functional attributes of the circulating vWF multimers (Thomas, 1996; Denis and Wagner, 1999; Brooks, 2000). The multimers, which are formed by the post-translational assembly of the parent dimeric molecule, are important in the haemostatic process because, at least in dogs, cats, pigs and people, the high molecular weight multimers are more active in their ability to support platelet adhesion than are low molecular weight multimers (Denis and Wagner, 1999). In ferrets, low molecular weight vWF multimers are the predominant plasma form of the protein (Hoogstraten-Miller et al., 1995). There appear to be conformational differences in the vWF protein among species since vWF of porcine and bovine origin, unlike human vWF, can aggregate human platelets in vitro without any other platelet agonist being present (Forbes and Prentice, 1973; Altieri et al., 1986). Because of the increased instability of FVIII, reduced plasma FVIII activity is one of the characteristics of reduced plasma vWF antigen levels in both dogs and people (Denis and Wagner, 1999). However, a similar correlation between FVIII activity and vWF antigen levels is not consistently observed in pigs (Fass et al., 1976).

Although homozygous deficiency of plasma FXI does not appear to be associated with reduced reproductive

efficiency in mice (Gailani et al., 1997) or dogs (Dodds and Kull, 1971; Knowler et al., 1994), it is associated with delayed ovulation and increased fetal loss in Holstein cattle (Liptrap et al., 1995). The decreased reproductive efficiency in clinically asymptomatic cows may explain why relatively few homozygous FXI deficient cows have been identified in dairy herds relative to the number of heterozygous FXI deficient animals (Gentry and Ross, 1995). The discrepancy in fertility rates in transgenic mice and dairy cows serves to illustrate the potential pitfall of extrapolating results of studies with laboratory animals to larger domestic animals.

3.3. Contact activation system

Several of the components of the classical contact activation pathway of coagulation, including FXII (Hageman factor), high molecular weight kininogen (HK) and prekallikrein (PK) do not appear in the revised coagulation scheme (Fig. 1). This group of proteins was initially considered to be important in thrombin formation after it was discovered that, when blood came into contact with a negatively charged foreign surface, FXII underwent a conformational change that enabled it to convert FXI to FXIa (Wachtfogel et al., 1993). This reaction still forms the basis for the laboratory test known as the activated partial thromboplastin time (APTT) that is used to evaluate abnormalities of the coagulation factors in plasma with the exception of FVII and FXIII. However, in vivo, activation of the contact system occurs independently of negatively charged surfaces (Gailani and Broze, 1991; Colman and Schmaier, 1997). It is postulated that the physiological equivalent to the negatively charged surface is the assembly of this group of proteins on cell membranes (Colman and Schmaier, 1997). Indeed, FXI activation can occur on the plasma membrane of activated platelets in the absence of FXII (Oliver et al., 1999). The contact activation coagulation hypothesis was further undermined by the fact that no haemostatic abnormalities occur in people with an inherited deficiency of either Factor XII, PK or HK (Kitchens, 2002). Similarly, FXII deficiency is an asymptomatic condition in dogs and cats (Green and White, 1977; Kier et al., 1980). For example, PK deficiency was discovered, fortuitously, in two mature dogs as a result of routine coagulation screening (Chinn et al., 1986; Lisciandro et al., 2000). However, it is possible that animals with reduced levels of FXII and PK are predisposed to developing haemorrhagic problems. In a Belgian stallion that bled excessively following castration plasma PK was found to be $<1\%$ of normal (Geor et al., 1990) and gastrointestinal haemorrhage in a one-year-old Chinese Shar Pei led to the discovery that the dog had a combined FXII and PK deficiency (Otto et al., 1991).

FXI is the only contact phase protein that clearly has a physiological role in blood coagulation (Bouma and Meijers, 2000). This conclusion is based not only on the ability of thrombin to activate FXI (Gailani and Broze, 1991) but also on the observations that people (Ragni et al., 1985; Bolton-Maggs et al., 1988), cattle (Gentry and Ross, 1995; Ogawa and Iga, 1998) and dogs (Dodds and Kull, 1971; Knowler et al., 1994) deficient in plasma FXI exhibit haemorrhagic episodes of varying severity and frequency.

4. Procoagulant protein differences among species

4.1. Fibrinogen

There is more information available about the biochemical and physiological aspects of fibrinogen than any other haemostatic protein. This is due, in part, to the fact that plasma fibrinogen levels are at least 20-fold higher than any of the other coagulation factors. For example, in human plasma normal fibrinogen levels are 2.0–4.0 g/L compared to 100 mg/L for prothrombin and 10, 5 and 0.5 mg/L for Factor X, Factor IX and Factor VII, respectively (Roberts and Tabares, 1995). Further, fibrinogen is one of the haemostatic proteins that is routinely assessed in veterinary medicine as a component of haematological evaluations. In all species plasma fibrinogen is synthesized in the liver and is released into the circulation as a molecule consisting of three non-identical polypeptide chains, designated as $A\alpha$, $B\beta$ and γ, that are linked by disulphide bridges (Lord, 1995; Gentry, 1999). Although the synthesis of each chain is controlled by a separate gene, only the $A\alpha$ chain appears to have structural diversity among species (Doolitte, 1973; Crabtree et al., 1985; Yang et al., 2000). Based on both structural and functional studies, it has been estimated that the fibrinogen molecule isolated from human, baboon, rabbit, dog, and rat plasma is evolutionary divergent from that of the fibrinogen molecule found in cow, pig, horse, goat, and sheep plasma (Henschen et al., 1983; Frost and Weigel, 1990).

Using a spectrophotometric method to detect clottable protein, plasma fibrinogen values have been estimated to range from 86% to 170% of normal human values in domestic and laboratory animals and in poultry (Lopaciuk et al., 1978). More recent studies have employed the modified thrombin clotting assays based on the Clauss method (Clauss, 1957). With this method cattle and water buffalo generally exhibit higher fibrinogen values (2.0–8.0 g/L) while the values for domestic cats and rabbits are generally lower (0.5–3.0 g/L). A fibrinogen range of 1.4–3.0 g/L was recorded in llama plasma (Morin et al., 1995) which is similar to the range reported for fish (Pavlidis et al., 1999) and avian species (Frost et al., 1999). Fibrinogen values of 4.2–4.4 and 4.1–5.1 g/L have been recorded for the iguana and Asian elephant, respectively (Kubalec et al., 2002; Gentry et al., 1996).

Unlike other haemostatic proteins, an increased rate of fibrinogenesis is a uniform response of the liver to hepatocyte damage induced by infectious, toxic, or metabolic agents. This response is translated into hyperfibrinogenaemia which is characteristic of a broad range of bacterial infections and other inflammatory conditions in vertebrates ranging from *Xenopus* (Bhattacharya et al., 1991), poultry (Espada et al., 1997), mice (Rofe et al., 1996), rabbits (Gentry et al., 1992), dogs (Eckersall and Conner, 1988; Otto et al., 2000), horses (Topper and Prasse, 1998a; Hulten and Demmers, 2002), cattle (Deldar et al., 1984), sheep (Fernandez et al., 1995; O'Brien et al., 1995) and exotic animals (Hawkey and Hart, 1987). The increased production of fibrinogen in response to inflammatory stimuli may be related to its role, and that of its thrombin-modified form fibrin, as a modulator of the inflammatory response. Fibrin(ogen) can enhance fibroblast migration and proliferation and facilitate leukocyte-endothelial cell adhesion and transmigration at inflammatory sites (Brown et al., 1993; Vogels et al., 1993; Languino et al., 1995).

4.2. Vitamin K-dependent proteins

The observation that vitamin K is an essential nutrient for normal haemostasis was first recognized in poultry as a result of feeding low fat diets to chickens (Dam, 1929). The association between haemorrhagic disease and the ingestion of mouldy corn by cattle (Campbell and Link, 1941) led to the discovery of the dicoumarol family of anticoagulant drugs. Because vitamin K is required for the synthesis of biologically functional forms of prothrombin and FVII, FIX and FX, it is perhaps not surprising that few inherited disorders related to defects in vitamin K metabolism have been observed in animals. A vitamin K-dependent coagulopathy has been reported in Devon Rex cats (Maddison et al., 1990; Soute et al., 1992; Littlewood et al., 1995), a Labrador Retriever (Mason et al., 2002), and in Rambouillet sheep (Baker et al., 1999). The haemorrhagic phenotype appears most severe in sheep. Lambs may have a greater sensitivity to conditions that influence vitamin K-dependent proteins because, compared to adults, fetal sheep, like fetal humans, have low vitamin K-dependent coagulation factors during the last trimester of gestation (Fantl and Ward, 1960; Moalic et al., 1989; Andrew et al., 1990). This is one of the reasons why lambs have been used as a model for the development of blood coagulation (Kisker et al., 1981) rather than other species such as the rabbit kit or calves who are born with adult levels of FVII, FIX and FX (Massicotte et al., 1986; Gentry et al., 1994).

Until recently the only laboratory techniques available for the quantitation of activity levels of specific coagulation factors were based on the ability of a test plasma to correct the clotting time of human plasma obtained from an individual with an inherited deficiency in one of the factors (Johnstone, 1988; Dodds, 1997). In veterinary practice, this type of assay system assumes that there is sufficient structural homology between the human proteins and those of other species that they can react interchangeably in the thrombin generating pathway. Plasma from most mammalian species will correct the prolonged clotting time of human factor-deficient plasma to a greater or lesser extent. Hence, this type of assay has utility in diagnostic laboratories in which haemostatic abnormalities are being evaluated, particularly when the activity in a test plasma sample can be compared to a matched species control sample. However, this type of assay is not necessarily reliable when the absolute activity for a non-human species is being determined. For example, using the coagulation correction time assay, prothrombin activity has been reported as 8–30% for avian plasma (Lewis, 1996) and 36–43% for sheep and cattle plasma (Karges et al., 1994) relative to human plasma. In contrast, when prothrombin is evaluated in chicken, sheep and bovine plasma with a direct activation chromogenic assay system, the prothrombin activity is estimated to be 87%, 44% and 121% of human reference plasma, respectively (Fig. 2). In this chromogenic assay, prothrombin is activated by specific cleavage with the enzyme Ecarin which is extracted from the venom of the saw-scaled viper (*Echis carinatus*). Prothrombin activity is quantified by an absorbance change in the reaction mixture

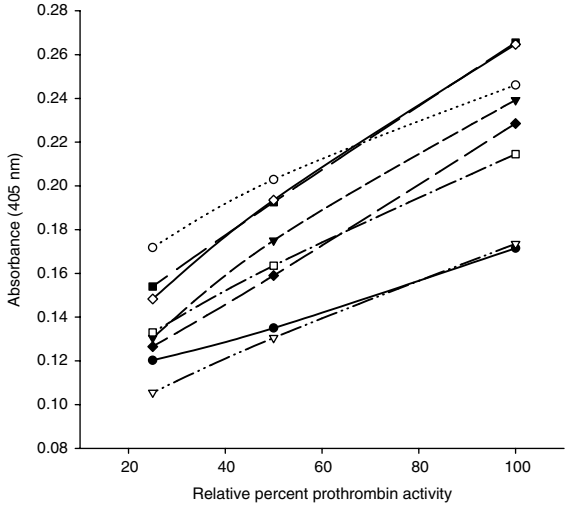

Fig. 2. Representative standard curves for prothrombin activity, assessed with a chromogenic assay, in serial dilutions of pooled citrated plasma from several species. A 100% value represent the prothrombin activity determined in a plasma sample diluted 10-fold. For clarity, the human reference plasma curve, which falls between that of the cow and elephant seal plasma, has been omitted.

when the activated prothrombin interacts with a synthetic substrate. As shown in Fig. 2, prothrombin activity in plasma from a broad range of species can be evaluated with this assay. The assay system is sensitive to alterations in plasma prothrombin activity as illustrated by the correlation in the reduction in substrate conversion as the dilution of the sample is increased. Moreover, the similarity of the slope of the curves suggests that the Ecarin enzyme can cleave prothrombin from each species in a similar manner. This conclusion is in agreement with those of an earlier study that used electrophoretic analysis to demonstrate that the activation of chicken and bovine prothrombin was similar (Walz, 1978).

The similarity in the response of the vertebrate prothrombin to direct activation may be related to the conservation among species of amino acid sequence around the reactive site. Although the conservation of the amino acid sequence for the complete prothrombin molecule is estimated at only 41%, there is no variance in the 10 glutamate residues that are critical for the formation of functionally active prothrombin which consistent with a common mechanism for vitamin K-dependent carboxylation (Banfield et al., 1994). Among the advantages of the prothrombin chromogenic assay is that, unlike the coagulation assay, it is not phospholipid-dependent and, at least for feline plasma, yields similar results whether plasma is prepared with either citrate or EDTA as the anticoagulant (Gentry and Christopher, 2001). Although the prothrombin chromogenic assay estimates both vitamin K-carboxylated and non-carboxylated vitamin K, it has proved to be effective in detecting prothrombin reduction in a dog with vitamin K deficiency and the subsequent increases in activity following vitamin K therapy (Mason et al., 2002).

Quantitative immunoassays using commercially available antibodies directed to specific coagulation proteins are increasing being utilized as diagnostic tools in human medicine. However, because the currently available antibodies are designed to react specifically with either human or mouse proteins, it appears that immunological assays will have limited use in veterinary medicine until species-specific antibodies are available (Ravanat et al., 1995; Munster et al., 2002).

Variable results for plasma FX activity are reported among species depending on whether a coagulation or a chromogenic assay is used. For example, in coagulant-type assays, plasma from reptiles and birds either fails to correct, or only partially corrects, the clotting time of human FX-deficient plasma (Belleville et al., 1982; Lewis, 1996; Frost et al., 1999). In contrast, the level of FX activity in avian and mammalian plasma appears to be equivalent when a chromogenic assay is employed. Activity values of 1.7 ± 0.5, 1.9 ± 0.7 and 1.9 ± 1.3 U/mg have been reported for chicken, sheep and human plasma, respectively (Frost et al., 1999). The chromogenic assay has also been shown to be effective in estimating Factor X activity in equine (Topper and Prasse, 1998b), canine (Mason et al., 2002), bovine (Roach et al., 2002) and feline (P.A. Gentry, unpublished data) plasma. In the FX chromogenic assay an enzyme extracted from the venom of the Russell's viper (*Vipera russelli*), RVV-X, specifically cleaves the same internal peptide bond in the FX molecule as does FVIIa and FIXa (Takeya et al., 1992). Because RVV can induce blood clot formation in fish, avian and mammalian plasma, it would appear that there is homology in the FX reactive site among vertebrates.

Little is known about the homology of the FVII and IX proteins among species. These proteins circulate in blood at extremely low levels which presents difficulties in obtaining sufficient blood from many species to permit their extraction and biochemical analysis. Currently there are no commercially available chromogenic assays for the determination of either FVII or FIX activity.

5. Haemostatic efficiency among vertebrates

The pioneer researchers in comparative haemostasis documented that both in vivo bleeding times and in vitro whole blood clotting times are similar in fish, birds and carnivores and, in each species, are shorter than in people (Hawkey, 1974; Lewis, 1996). These observations are different from the results of most studies that have compared the rates of in vitro fibrin formation by the Tissue Factor (Extrinsic) pathway and the Amplification (Intrinsic or Contact Activation) pathways (Fig. 1) using non-species specific reagents. In diagnostic laboratories the Tissue Factor pathway is evaluated by the prothrombin time (PT) assay in which a tissue factor-phospholipid-calcium mixture or "thromboplastin" is used to initiate fibrin formation in platelet-depleted plasma. The species specificity of tissue thromboplastin preparations has been recognized since the early period of coagulation research (Moore et al., 1935; Stormorken, 1957; Irsigler et al., 1965). Several studies have demonstrated that thromboplastin preparations appear to be most efficient at inducing thrombin production when added to homologous plasma (Janson et al., 1984; Karges et al., 1994; Frost et al., 1999; Pavlidis et al., 1999; Thomson et al., 2002). At present, the most widely used commercially available thromboplastin reagents are derived from rabbit tissues. These reagents are only adequate for evaluating TF pathway abnormalities in domestic animals when the clotting time of a patient's plasma is compared to control values obtained with the same reagent for the same species (Meyers et al., 1987; Parry, 1989; Mischke and Nolte, 1997). Further, Mischke et al. (2003) compared the values obtained for FVII

in canine plasma measured in the same assay system with several different thromboplastin reagents and found a wide range of sensitivities.

Reagent formulations are also problematic in the evaluation of the Amplification or Contact activation pathway with the activated partial thromboplastin time (APTT) assay. In this assay thrombin generation is initiated by the addition of a non-physiological, negatively charged compound, e.g., celite, kaolin or ellagic acid, suspended in a phospholipid mixture to platelet-depleted plasma. The rationale for the assay is that the artificial surface activates FXII which then converts FXI to FXIa that, in turn, initiates the formation of the "tenase" complex by activating FIX (Fig. 1). It has been proposed that reptiles, birds and cetaceans lack FXII and FXI, because not only does their plasma exhibit prolonged APTT results compared to mammals, but also their plasma fails to correct the clotting time of human FXII deficient or FXI deficient plasma in a modified APTT assay system (Dodds, 1981; Belleville et al., 1982; Lewis, 1996). It is possible that this apparent discrepancy among vertebrate plasma is due to a lack of homology of the FXII and FXI proteins among species. It remains to be established whether the prolonged APTT results for non-mammalian species is due to the inability of the artificial surface component of the reagent mixture to activate the FXII molecule in an analogous fashion as occurs for mammalian FXII.

Even among mammalian plasmas a discrepancy between the ability to correct the clotting time of human FXII deficient plasma and their ability to immunologically cross-react with antibodies to human, bovine or rat FXII has been noted (Saito and Ratnoff, 1979). Differences in cross-reactivity in FXI is also evidenced by the finding that, as occurs with Asian elephant plasma (Gentry et al., 1996), plasma from Elephant seals will correct the clotting time of human FXI-deficient plasma but not bovine FXI-deficient plasma (P.A. Gentry, unpublished data). However, like the PT assay, the APTT assay has utility for evaluating overall FVIII and FIX activity within a species, especially for the identification of FVIII and FIX activity in plasmas of haemophilic dogs (Mischke, 2000a,b).

6. Thrombophilia

Thrombophilia in animals is generally associated with pathophysiological conditions that cause alterations in blood flow, vascular disorders and/or haemostatic abnormalities (Darien, 2000; Blann and Lip, 2001). For example, in cats, thromboembolism is frequently associated with cardiomyopathy (Welles et al., 1994; Schoeman, 1999). One of the underlying causes is thought to be turbulent blood flow through the heart chambers and valves that induces platelet activation and thrombus formation. The clot, or thrombus, may be dislodged by the flowing blood to become lodged as an embolus in other areas of the circulation such as the distal carotid artery (Schoeman, 1999). An additional contributory factor to thrombus formation in these cats with cardiomyopathy may be the increased responsiveness of their platelets to agonist stimulation (Welles et al., 1994; Helenski and Ross, 1987). Thrombophlebitis has been reported in horses following long-term indwelling catheter use (Lankveld et al., 2001). In these animals, it is likely that the thrombosis is the result of a combination of disturbance of blood flow and activation of the coagulation system. A hypercoagulable condition induced by inflammatory mediators has been postulated as the cause of thrombosis of limb arteries in foals with Gram-negative bacteraemia (Triplett et al., 1996; Brianceau and Divers, 2001). A decreased blood supply to the laminae and platelet-dependent thrombosis of laminar vessels are observed at the onset of lameness in experimentally induced equine laminitis (Weiss et al., 1994, 1998). However, in equine laminitis, the decreased platelet survival time and the increased platelet deposition in the hoof wall do not appear to be associated with systemic activation of coagulation (Weiss et al., 1996). Blood vessels are the principle target of equine arteritis virus (Del Piero, 2000). Vascular damage induced by the virus is likely one of the causes of the thrombosis that can be a clinical manifestation of infected horses.

There is a high incidence of clinical thrombosis or phlebitis in dogs with canine parvoviral enteritis (Otto et al., 2000). In a retrospective study of dogs necropsied during a two-year period in one pathology department, pulmonary thromboembolism was one of the most prevalent diseases identified (LaRue and Murtaugh, 1990). The majority of dogs were middle-aged or older and all had at least one underlying disease process that is associated with haemostatic abnormalities. It has been shown that fibrin deposition in the lungs of cattle with pneumonic pasteurellosis is induced by a combination of TF expression on the surface of endothelial cells and monocytes (Weiss et al., 1995; Rashid et al., 1997) and the activation of plate- lets (Nyarko et al., 1998) by the infectious agent, *Pasteurella mannheimia*. The importance of inflammatory mediators in the systemic activation of coagulation with resulting deposition of microthrombi within the vasculature is becoming increasing appreciated in veterinary and human medicine (Weiss and Rashid, 1998; Esmon et al., 1999; Kerr, 2001) as are the consequences of interactions between blood platelets and inflammatory cells (Coomber et al., 2001).

A genetic predisposition to developing thrombosis is recognized among the human population (Rosendaal, 1999). Among the genetic components are deficiencies

in the natural circulating anticoagulant proteins, such as antithrombin, protein C and protein S, or mutations in Factor V and prothrombin that all result in the upregulation or dysregulation of thrombin formation (Sykes et al., 2000; McGlennen and Key, 2002; Ranguelov et al., 2002). Inherited abnormalities of this type do not appear to have been reported in domestic animals. Whether this is due to the lack of adequate diagnostic detection systems or is a true reflection of the lower incidence of thrombosis in domestic animal compared to people remains to be determined. There is some evidence, however, to suggest that animals may be at lower risk of developing thrombotic type coagulopathies. For example, although pregnancy is recognized as one of the risk factors for thrombosis in women (Rosendaal, 1999; Davis, 2000) it is not generally associated with haemostatic abnormalities in non-human vertebrates. This difference may be due, at least in part, to the observation that hyper-coagulable states develop in women but not in other mammals during pregnancy.

Increased circulating fibrinogen levels and FVIII activity are a recognized risk factor for thrombotic problems in people (Gerbasi et al., 1990; Davis, 2000; Chandler et al., 2002). The circulating levels of these proteins, along with FVII, FIX, FX and vWF, gradually increase throughout the human gestation period (Stirling et al., 1984; Hellgren, 1996; Davis, 2000). In contrast, no marked alterations in in the circulating level of any of the coagulation factors, are observed in cows (Gentry et al., 1979; Heuwieser et al., 1990), sows (Liptrap and Gentry, 1984), mares (Sieme et al., 1991), camels (Hussein et al., 1992), or Asian Elephants (P.A. Gentry, unpublished data) during pregnancy. In dogs, only fibrinogen levels exhibit a transient increase at mid-gestation (Gentry and Liptrap, 1981; Concannon et al., 1996; Gunzel-Apel et al., 1997).

7. Future directions

Based on available information, it appears that the biochemical processes of thrombin generation and fibrin clot formation are similar across species. The current concept that the tissue factor pathway is the primary initiating pathway in the haemostatic process is compatible with the emerging biological roles that the various enzyme components of this pathway have in non-coagulation biological reactions. For example, not only is thrombin, and its immediate upstream serine proteases, FXa and FVIIa, involved in inflammation and tissue remodelling, but they also have critical roles in angiogenesis (Carmeliet, 2001; Patterson et al., 2001; Rickles and Falanga, 2001; Versteeg et al., 2003). These non-haemostatic functions of the serine proteases are mediated through their interaction with a family of specific cell-surface receptors known as proteinase-activated receptors or PARs (Bohm et al., 1998; Coughlin, 2000; Petersen et al., 2000; Riewald and Ruf, 2002). Evidence is emerging indicating that TF, a member of the cytokine type II or interferon receptor family (Peppelenbosch et al., 2003), may also have a role in coagulation-independent embryonic and tumorigenic angiogenesis (Versteeg et al., 2003; Griffin et al., 2001; Rickles and Falanga, 2001). These findings, that to date are largely based on experimental models, raise interesting questions regarding the potential biological roles of these proteins and their receptors in both normal physiology and pathophysiology and point to new avenues of investigation for this group of haemostatic proteins in veterinary medicine.

During the past decade many of the advances in our understanding of the normal physiological function of haemostatic proteins have come from studies using genetically modified mice rather than the type of studies that were done during the 1960s and 1970s with companion and domestic animal models. As a result, there is limited information about the functional significance of several of the more recently discovered haemostatic proteins except in human and murine plasma. For example, the role of the thrombomodulin–protein C–proteins S anticoagulant system as a link between coagulation and inflammation is well recognized in human medicine (Cicala and Cirino, 1998; Esmon, 2001) but it has not been extensively examined in veterinary medicine. Likewise, the association between plasma tissue factor pathway inhibitor (TFPI) activity and the attenuation of pathological thrombus formation has been established in human patients and in animal models of intravascular thrombosis (Golino et al., 2002) but has not been explored in veterinary medicine. Part of the reason for this lack of information is the absence of commercially available reagents that are satisfactory for evaluating these haemostatic proteins in veterinary diagnostic laboratories. In the absence of a broad panel of reliable laboratory assay procedures, it will likely be some time before the coagulant-dependent and coagulation-independent roles of the various haemostatic proteins are established in veterinary medicine.

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