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Review article

Review: The mechanism of blood coagulation, its disorders and measurement in poultry

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ABSTRACT

Intensive genetic selection has improved productive traits in poultry and contributed to changes in systemic metabolism; however, their blood coagulation processes have received little study. The precise physiological mechanisms of haemostasis in birds remain poorly understood, but blood clotting is believed to be governed by an extrinsic tissue factor-dependent pathway, with some residual intrinsic pathway serving an ancillary function. Disorders of haemostasis are a common pathology in poultry rearing, manifested by bleeding, which most often occurs in the muscles, intramuscular fat, connective tissue and internal organs. Efficient diagnosis of haemostatic disorders in poultry remains an ongoing problem. The diagnostic methods currently in use in veterinary medicine are inadequate for evaluating haemostatic disorders. The optimisation of coagulometric methods and the availability of species-specific reagents remain significant obstacles. Furthermore, although vitamin K is essential for the synthesis of extrinsic coagulation factors and interacts with vitamin D in bone formation, it is frequently deficient in birds. The objective of the paper is to present the current state of knowledge of haemostatic disorders in poultry, and to stress the need to develop more detailed laboratory procedures and methods of producing species-specific reagents for determination of haemostatic parameters to deepen the understanding of blood clotting in birds.

1. Introduction

Intensive genetic selection has improved productive traits in poultry and contributed to changes in systemic metabolism, including haemostasis (Buzala et al., 2014, 2015; Buzala and Janicki, 2016). Haemostasis is sustained by a set of physiological mechanisms that maintain the fluidity of circulating blood in the vascular bed and stop blood loss following injury to blood vessels (Gentry, 2004; Kim et al., 2009). The environmental factors and genetic selection associated with modern poultry breeding have prompted further studies to better understand the haemostatic system of the birds (Frost et al., 2000; Thomson et al., 2002). Common pathologies observed in poultry production are infarction and fatty liver haemorrhagic syndrome, which lead to disturbances in blood clotting mechanisms (Doerr et al., 1974, 1976, 1981a, 1981b; Doerr and Hamilton, 1981; Fernandez et al., 1995; Shibatani et al., 1997; Thomson et al., 2002, 2003; Muramoto et al., 2006; Yeh et al., 2008, 2009; Nazifi et al., 2010; Pliszczak-Krol et al., 2012; Zeryehun et al., 2012). They are characterized by bleeding, which most often occurs in muscles, intramuscular fat and connective tissue (Kranen et al., 2000a, 2000b; Gentry et al., 2008), as well as internal organs such as the liver, intestine, and bursa of Fabricius (Doerr et al., 1975; Pliszczak-Krol et al., 2012). Increased mortality and defects in the carcass resulting from haemostatic disorders are problems of considerable economic importance to the poultry industry (Doerr et al., 1975; Thomson et al., 2002).

The efficient diagnosis of haemostatic disorders in poultry remains an ongoing problem. As the methods used by veterinary medicine to diagnose and monitor haemostatic disturbances are calibrated for mammals, the optimisation of coagulometric methods and the availability of species-specific reagents for birds still remain an important challenge (Doerr et al., 1975; Pliszczak-Krol et al., 2012; Guddorf et al., 2014).

The aim of this review is present the current understanding of haemostasis in poultry, including a description of the possible diagnosis of physiopathological conditions in this area.

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2. Platelets vs. Thrombocytes

Platelets are the smallest morphotic elements of mammalian blood (2–3 μm in diameter). Despite lacking a nucleus, they contain conventional cellular organelles, including mitochondria, which enable them to have an active metabolism. Platelets have a highly organized cytoskeleton, specific secretory granules and a unique system of membrane receptors conditioning their high reactivity. The main role is to maintain haemostasis, but they also perform important functions in inflammation, immune processes and the progression of neoplasms. The formation of platelets is the final stage of differentiation of gigantic polynuclear cells called megakaryocytes (50–100 μm in diameter). Platelets are considered to be terminally differentiated cells, which are not capable of further cell divisions, and are found throughout all existing groups of mammals: eutherians, marsupials and monotremes (Lewis et al., 1968; Barbour, 1972; Tanaka et al., 1988; Geraghty et al., 2011). The evolution of platelets has enabled clots to form faster and slowed blood loss in case of injury, but are also responsible for an increased risk of thromboembolic diseases.

In other vertebrates, including birds, cellular haemostasis is governed by the activity of nucleated larger thrombocytes (avian thrombocytes 5–8 μm in diameter), which have a much lower reactivity than platelets (Stalsberg and Prydz, 1963; Gallo et al., 2015). Avian thrombocytes have multiple mitochondria, dense granules, an irregular shape and are similar to small leukocytes. They are formed in bone marrow from thromboblast-like platelet-generating megakaryocytes from megakaryoblasts. Thrombocytes share many features with platelets: they are activated by thrombin and adhere to fibrinogen, and release serotonin and pro-inflammatory cytokines (Meseguer et al., 2002). They have homologous proteins to those present in the platelets of mammals (Wachowicz and Krajewski, 1979; Wachowicz et al., 1981, 1988).

3. Blood coagulation pathways and cell-based coagulation

The classical blood coagulation cascade of mammals includes the extrinsic pathway, dependent on tissue factor, the intrinsic pathway, based around contact activation on a negatively-charged surface, and the common pathway which operates by the activation of thrombin by coagulation factor X and formation of fibrin clots. Although the pathways are closely related and usually act simultaneously, it is difficult to distinguish them. However, the Y-cascade model is still used to describe the processes occurring during blood clotting in animals. This classical coagulation model has evolved to include three phases: initiation, amplification, and the effector or propagation phase. According to the latest cell-based blood coagulation theory in humans (Hoffman et al., 1996; Hoffman and Monroe, 2001; Smith, 2009), the main coagulation component is the tissue factor-dependent pathway, with the intrinsic pathway (dependent on contact factors XI, XII, prekallikrein and high molecular weight kininogen) serving an ancillary role (Wheeler and Rice, 2010). In birds and other non-mammalian vertebrates (Doolittle et al., 2008), the tissue factor-dependent pathway is arguably essential for the thrombin formation process (Fig. 1). However, as birds lack contact factors XI and XII (Doerr et al., 1974; Doerr and Hamilton, 1981; Thomson et al., 2002; Ponczek et al., 2008; Nevill, 2009), the presence of the intrinsic factor is still a matter of debate.

3.1. Tissue factor-dependent pathway

Vascular endothelial damage caused by tissue damage and inflammatory factors result in the expression of tissue factor (TF, thromboplastin, factor III, CD142) on the surface of the cell membrane, which is responsible for activation of factor VII (Doerr and Hamilton, 1981; Thomson et al., 2002). TF is a lipid-dependent transmembrane glycoprotein essential for the maintenance of normal haemostasis

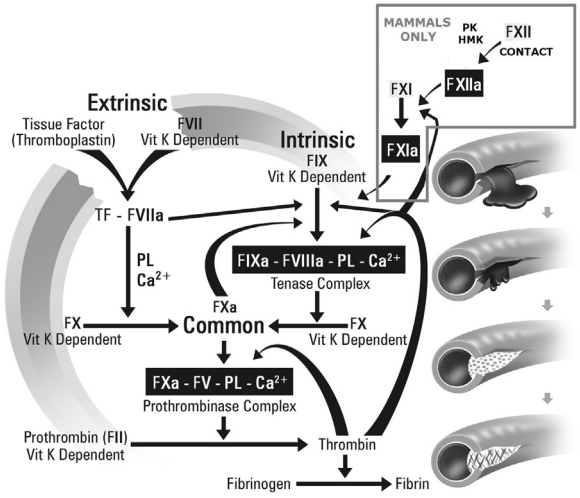

Fig. 1. Blood coagulation pathways in birds (F= Factor, HMK=High-molecular-weight kininogen, PL=Phospholipids, PK= Prekallikrein).

and the development of blood vessels (Frost et al., 1999; Gentry, 2004; Takahira et al., 2012). It is expressed in many cells, but mainly the monocytes and the cells of blood vessels. TF is released from these cells in response to trauma or the stimulation of vascular endothelial cells and monocytes by pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) (Thomson et al., 2002; Muramoto et al., 2006). The released TF interacts with circulating factor VII to form the enzymatically reactive TF-FVIIa complex. With the participation of phospholipids and calcium ions, this complex transforms factor X into the active form, FXa (Gentry, 2004). The activity of the TF-FVII complex is strictly regulated by TFPI (tissue factor pathway inhibitor), which can reversibly inhibit factor Xa, and inactivate the VIIa/TF complex on cell membranes when in complex with Xa (Doolittle et al., 2008; Ponczek et al., 2008; Takahira et al., 2012). The role of TFPI has been thoroughly studied in humans, but little is known about the presence and function of TFPI in the blood of domestic animals, including poultry (Gentry, 2004).

3.2. Intrinsic pathway

In birds, the residual intrinsic pathway is activated by factor IX through the factor VIIa/TF complex. Factor IX is a result of duplication of the gene for factor X and is absent in simple jawless vertebrates like lampreys (Doolittle et al., 2008). This common relationship enables the VIIa/TF complex to activate both coagulation factors IX and X. Factor IXa, factor VIIIa and calcium ions, together with phospholipids, form a tenase complex on the surface of activated thrombocytes (Fig. 1), which converts factor X to its active form Xa. Formation of the active tenase complex may be also facilitated by thrombin as a result of a feedback effect through activation of factor VIII (FVIIIa), which dissociates from the complex with von Willebrand's factor (vWF) (Thomson et al., 2002; Gentry, 2004; Ponczek et al., 2008). The binding of FVIII with factor vWF increases the half-life of factor VIII in plasma, by protecting it from proteolytic degradation (Gentry, 2004). It is difficult to present this system as full intrinsic activation with contact activation on a negatively-charged surface, because neither coagulation factor XI nor XII is present in birds.

3.3. Common pathway

The common pathway is activated by FXa, which is generated by the tissue factor-dependent and intrinsic pathways. FXa forms the prothrombinase complex (Fig. 1) by binding to the phospholipids of blood platelets or thrombocytes together with FVa in the presence of