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Review

Cobalamin in companion animals: Diagnostic marker, deficiency states and therapeutic implications

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ABSTRACT

Measurement of the water-soluble vitamin cobalamin has long been of interest as a marker of gastrointestinal disease in companion animals due to the highly localized presence of cobalamin receptors in the ileum. An increasing body of evidence suggests that cobalamin deficiency is an important co-morbidity in many companion animal patients with gastrointestinal and pancreatic disease. Congenital disorders of cobalamin absorption and cellular metabolism are also increasingly recognized in companion animal breeds. The early recognition of these disorders and timely treatment with parenteral cobalamin can be life-saving. In this article, the normal mechanisms of cobalamin absorption, the use of cobalamin as a marker of intestinal disease and data on the prevalence of hypocobalaminemia in a variety of diseases are described. The prognostic impact of and rational therapy for hypocobalaminemia in domestic animals are discussed.

Introduction

Cobalamin is a member of the B-group of water-soluble vitamins. Commonly the vitamin is known as B_{12}, however the term 'vitamin B_{12}' is a generic descriptor of all corrinoid compounds that exhibit qualitatively similar biological activity to cyanocobalamin (Anonymous, 1986). Not all of the corrinoid compounds are biologically available to eukaryotes, thus the word 'cobalamin' more accurately describes the corrinoid compounds with biological activity in humans and species of veterinary interest.

The earliest recognition of cobalamin as a vitamin came from experimental studies of the role of diet in red cell regeneration following induction of anemia by serial phlebotomy of dogs. Working in the 1920s, George Whipple, the American physician and pathologist, observed that feeding dogs a liver-based diet resulted in more rapid red cell regeneration. George Minot and William Murphy built upon these observations to successfully treat human patients with pernicious anemia using liver-based diets. Whipple, Minot and Murphy subsequently shared the 1934 Nobel Prize in Physiology or Medicine '*for their discoveries concerning liver therapy in cases of anaemia*',[1] although at that time it was still unclear what the 'liver factor' actually was.

The physiologist William Castle (1897–1990) subsequently established that the stomachs of patients with pernicious anemia were failing to produce an 'intrinsic factor' that was necessary for the absorption of cobalamin; this glycoprotein is still known as intrinsic factor to this day. A period of 22 years transpired between Minot and Murphy's description of the 'liver diet' for pernicious anemia and the isolation, crystallization and final determination of the structure of cobalamin, with near simultaneous publications from American and English groups (Chanarin, 2000).

Cobalamin absorption and biochemical roles

Cobalamin is absorbed from the diet through a complex, receptor mediated process. This process is illustrated in Fig. 1. Dietary cobalamin complexed to protein in the diet is liberated in the stomach by pepsinogens and gastric acid. Immediately after the cobalamin is released, it is bound to gastric and salivary 'R-proteins', which carry the cobalamin into the duodenum. In the duodenum, the R-protein–cobalamin complex is broken down by pancreatic proteases and the cobalamin is then complexed with intrinsic factor. The major site of intrinsic factor synthesis varies between species. In humans, the gastric mucosa is the major site, while dogs produce intrinsic factor in both the stomach and the pancreas (Batt et al., 1989). The domestic cat synthesizes intrinsic factor in the exocrine pancreas exclusively (Fyfe, 1993).

Uptake of cobalamin from the gastrointestinal lumen is via a cobalamin/intrinsic factor complex receptor present only in the ileum. This receptor is a complex with at least two subunits, the proteins amnionless and cubilin (Fyfe et al., 2004). Following mucosal absorption, cobalamin is transported to the tissues complexed with yet another binding protein, transcobalamin II

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[1] See: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1934/index.html (Accessed 17 January 2013).

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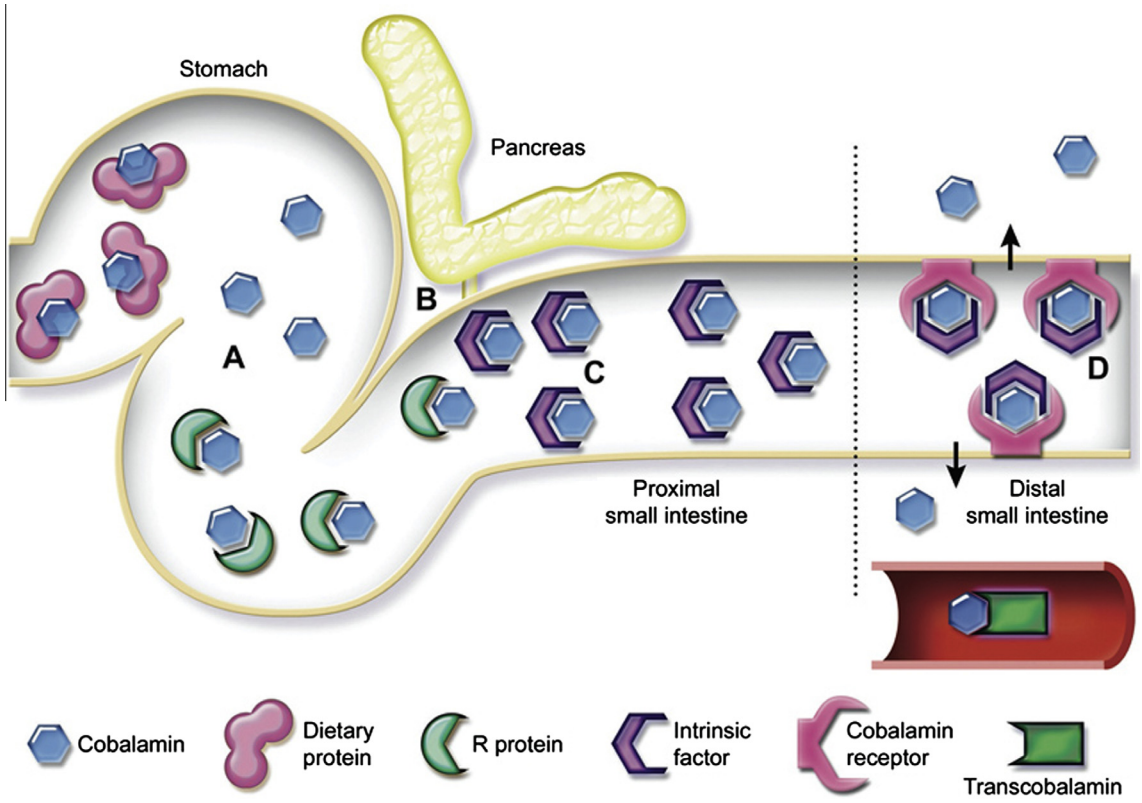

Fig. 1. Diagrammatic representation of the mode of absorption of cobalamin in carnivores. Note that normal absorption of cobalamin requires adequate function of the stomach (acid, proteases, intrinsic factor), exocrine pancreas (intrinsic factor, proteases) and ileal mucosa (cobalamin plus intrinsic factor receptors). Reproduced from Suchodolski and Steiner (2003).

(Banerjee, 2006). Various disorders in intracellular cobalamin metabolism have been described, but discussion of these is outside the scope of the current review, although they are well described by Banerjee (2006).

The biochemical role of cobalamin is as a cofactor for several enzymes responsible for transfer of single carbon moieties (such as methyl groups, $-CH_3$). In prokaryotes, cobalamin is a cofactor for a diverse collection of enzyme families including isomerases, methlytransferases and dehalogenases (Banerjee and Ragsdale, 2003). In mammalian species, only two enzymes are known to be cobalamin-dependent, namely, methionine synthase (a methyltransferase) and methylmalonyl-CoA mutase (an isomerase). Methionine synthase catalyzes the transfer of a methyl group to S-adenosyl-homocysteine, generating S-adenosyl-methionine and hence methionine, while methylmalonyl-CoA mutase catalyzes the isomerization of methlymalonyl-CoA to succinyl-CoA, which then enters the citric acid cycle (Banerjee and Ragsdale, 2003).

Biochemical consequences of cobalamin deficiency

Deficiency of cobalamin in mammalian species leads to alterations in the activity of cobalamin-dependent enzymes and accumulation of substrates or products of alternative metabolic pathways. In humans, cobalamin deficiency can be associated with a resting hyperhomocysteinemia, resulting from reduced activity of the methionine synthase enzyme.

This association between cobalamin deficiency and hyperhomocysteinemia has received significant attention in humans, as hyperhomocysteinemia has been proposed to be an independent risk factor for atherosclerotic disease, although this is an area of current controversy (Smulders and Blom, 2011). The relationship between serum cobalamin, homocysteine and cardiovascular disease has received relatively little attention in veterinary species. One study reported that cats with arteriothromboembolism and those with cardiomyopathy had lower serum cobalamin concentrations than healthy controls, but this study found no differences in plasma homocysteine concentrations between these groups (McMichael et al., 2000). In cats, hyperhomocysteinemia is not typically seen in sera from fasted cats, even when serum cobalamin concentrations are extremely low or undetectable (Ruaux et al., 2001). This might reflect the greater dietary intake of methionine in the cat and thus reduced reliance on methionine synthase to replenish methionine (Ruaux et al., 2001).

Reduced activity of methylmalonyl-CoA mutase leads to an accumulation of methylmalonyl-CoA, which subsequently feeds back on a branch point in the terminal degradation of several amino acids, leading to the increased production of methylmalonic acid (MMA). This MMA is subsequently excreted in the urine. Cobalamin deficiency in humans is also associated with methylmalonic acidemia and methylmalonylaciduria (Herrmann and Obeid, 2012). Cats with severely subnormal serum cobalamin concentrations typically show extreme elevations in serum MMA concentrations; in some cases a 50-fold elevation over the highest normal value can be documented. Similar findings have been reported in the Shar Pei dog in association with a breed-related cobalamin absorption disorder and in dogs of all breeds with presumed gastrointestinal disease (Ruaux et al., 2001; Berghoff et al., 2011; Bishop et al., 2011).

Relationships between hypocobalaminemia and cobalamin deficiency

Cobalamin-dependant reactions in eukaryotes occur in the mitochondria and the serum concentration of cobalamin is not