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Editorial

Birds as Pathology-Free Models of Type II Diabetes

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Editorial

In mammals, chronically elevated concentrations of blood glucose (chronic hyperglycemia) and decreased insulin levels can ultimately lead to Type 2 Diabetes Mellitus (T2DM) and its associated complications. In contrast, birds have significantly higher blood glucose concentrations than mammals of similar body mass (1.5~2 times) and yet are able to resist the regulation of glucose by insulin without any adverse effects [1]. Most avian species for which the relevant data are available appear to possess specialized mechanisms to enhance fatty acid transport and oxidation during flight [2,3]. These are similar to the way energy is utilized by diabetic humans who are unable to efficiently increase glucose utilization and consequently rely more on fatty acid oxidation when carbohydrates are plentiful [4]. To the best of our knowledge, the underlying mechanism regulating glucose and lipid hemostasis in birds has yet to be clarified. Several aspects of glucose regulation in birds are, however, worth highlighting, and may contribute to better understanding the pathogenesis and treatment of T2DM, and its associated complications, in humans.

Higher, but better-controlled, blood glucose concentrations

Birds have significantly higher blood glucose concentrations than other vertebrates of similar body mass [1,5]. Furthermore, they can maintain higher glucose concentrations within tight homeostatic limits regardless of food restriction, fasting, long-distance migration, or changes in photoperiod [1,6,7]. This ability to maintain higher glucose levels is thought to be correlated with the markedly higher standard metabolic rate (SMR) and body temperature of birds compared to other vertebrates, which are necessary to meet the energetic requirements of powered flight [8,9].

Birds have significantly lower plasma insulin levels (~10 times), but higher pancreas glucagon levels (8~10 times), than mammals [10]. Furthermore, the glucose metabolism of birds appears to be relatively insensitive to insulin (e.g. lipolysis, hepatic glycogenolysis, glycolysis or gluconeogenesis) but sensitive to glucagon (e.g. lipolysis, glycogenolysis or gluconeogenesis), compared to that of mammals [6]. In birds, hyperglycemia results from the glucagon activation of liver glycogenolysis (reviewed by [1]). Given that birds store little glycogen, amino acids produced by proteolysis in migratory species are key intermediates for replenishing glucose [3]. Therefore, the phenomenon of 'glucagon-driven' glucose hemostasis in birds is thought to be responsible for their stable and well-controlled blood glucose levels [5].

Lower levels of glycated hemoglobin

Although high glucose levels are known to increase glycosylated hemoglobin levels [5,7] birds have low levels of glycosylated hemoglobin relative to mammals [11]. Although the mechanism underlying the anti-glycation defenses of birds remains largely unknown, higher concentrations of reactive carbonyl-scavengers and/or transglycating agents, e.g. taurine (~6 fold) and other free amino acids (~4 fold), and lower levels of methylglyoxal (MG; undetectable), than mammals are thought to provide effective defenses against glycation and advanced glycation end-product (AGEs) formation (via Maillard reaction) [12,13]. Szwergold and Miller (2014) speculated that the Maillard reaction–related characteristics of birds may contribute to their ability to successfully cope with chronic hyperglycemia, and highlighted that birds could be a potential model for preventing diabetic complications through minimizing the production, and maximizing the elimination, of MG by detoxification or scavenging [12].

Loss of glucose and lipid metabolism related-genes

The loss of both protein-coding and non-coding genes in birds is a remarkable feature that is thought to be related to their evolution of metabolically-costly, powered flight [14,15]. A previous study has shown that birds have lost four genes encoding adipokines; one enhancing insulin sensitivity and three that inhibit it [16]. Although birds lack the receptor gene for AGEs that is present in mammals [17], they can nonetheless reduce the glycation of serum albumin in the presence of naturally high blood glucose concentrations relative to mammals [18-20]. Furthermore, birds lack the insulin-responsive glucose transport protein 4 (GLUT4), which is present in mammalian adipose tissue, cardiac and skeletal muscle (down regulated in adipose-tissue GLUT4 under fasting conditions and up regulated following feeding [1,21]). Therefore, the lack of several genes in birds that are reported to control the glucose and lipids metabolism of mammals can explain, to some extent, why high concentrations of blood glucose do not cause the hyperglycemia-related complications observed in mammals.

Compared with mammals, the mechanisms that allow birds to maintain such high blood glucose levels and an enhanced lipid metabolism have yet to be clarified. However, in recent years, ornithologists have taken the first steps towards obtaining basic information on the ecophysiology, endocrinology, and genome evolution of the avian energetic metabolism [12,18,22-29]. Such information is essential, not only for uncovering the regulatory mechanism of glucose and lipid metabolism in birds (especially free-

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living birds), but also for improving our understanding of the etiology of humanT2DM. Therefore, the unique attributes of the energetic metabolism of birds could hold the key to developing a "pathology-free model of T2DM" in the field of both zoology and endocrinology [12,22].

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