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Dietary metformin effects on in vitro and in vivo metabolism in the chicken☆

Robert W. Rosebrough*, Christopher M. Ashwell

Growth Biology Laboratory, Animal and Natural Resources Institute, United States Department of Agriculture-Agricultural Research Service, Beltsville Agricultural Research Center, Beltsville, MD 20705, USA

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Abstract

Chickens were fed diets containing 0, 0.25, 0.5, and 1 and 0, 2.5, 5, and 10 g metformin (MET)/kg diet in 2 separate experiments to determine whether MET (1,1 dimethylbiguanidine hydrochloride) regulated plasma glucose and, possibly, feed intake in broiler chickens. Feed intakes in the first experiment were equal, but, in the second experiment, MET at 5 and 10 g/kg reduced feed intake. The first series of diets had no effect on plasma glucose and lactate. The second series of dietary treatments did not affect plasma glucose but did increase plasma lactate, uric acid, and triglycerides linearly. In the second experiment, there were significant decreases in lipogenesis that accompanied increasing doses of MET. The increase in plasma lactic acid suggests that MET stimulates pyruvate kinase in the chicken, as it does in mammals. The lack of effect on plasma glucose also suggests that regulation occurs downstream of pyruvate in the chicken. These findings may explain MET's ability to reduce hepatic triglyceride synthesis and suppress appetite.
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1. Introduction

There are many agents used to control blood glucose and insulin intolerance in diabetics. Some of these agents (biguanides) improve insulin sensitivity of diabetic tissue [1]. Insulin

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* Corresponding author. Fax: +1 301 504 8623.

E-mail address: rosebro@anri.barc.usda.gov (R.W. Rosebrough).

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levels are low in chickens [2] with unknown metabolic effects. The relationship between plasma glucose and appetite is poorly understood in poultry. Exogenous hormone treatments have not resulted in marked changes in either feed intake or plasma glucose. Chickens are resistant to treatments that alter both plasma glucose and appetite in mammals. Recently, Ashwell and McMurtry [3] found that an acute dose of the biguanide metformin (MET) decreased food consumption as well as plasma glucose, insulin, and triglycerides. This observation supported some relationship between plasma glucose and food consumption by chickens.

As previously mentioned, a biguanide (MET) lowered plasma glucose levels in noninsulin-dependent human diabetics. The mechanism of action remains unknown, although, in some cases, reduction of hepatic glucose output may be the basis for MET's benefit in diabetes. The balance of the evidence suggests inhibition of gluconeogenesis [4-6]. Other sets of work indicate that biguanides reduce hyperglycemia by increasing insulin sensitivity, decreasing glucose absorption, and inhibiting hepatic gluconeogenesis. Studies have examined the effect of biguanides and MET in particular on hepatic glucose production and muscle glucose use and have yielded conflicting results and little information about the action of MET on lactate turnover and gluconeogenesis from lactate. Metformin has no effect on the rate of lactate turnover or gluconeogenesis from lactate [7]. In contrast, there is an increased flux through pyruvate kinase in MET-treated cells, suggesting allosteric activation of pyruvate kinase by fructose-1,6-diphosphate.

More recent work suggests that MET improves insulin-mediated glucose transport in isolated muscles. In contrast, in the absence of insulin no changes in basal glucose transport activity were observed [1]. These authors reported that part of the beneficial effect of MET on insulin resistance results from facilitating the hormone-stimulating effect on glucose transport in peripheral tissues (mainly skeletal muscle). In contrast to mammals, glucose production is the main method of regulating plasma glucose. The hypothesis tested in the experiments in this report was that chemically altering plasma glucose by inhibiting glucose production might decrease plasma glucose, change feed intake, and affect some indices of intermediary metabolism. In vitro lipogenesis (IVL) was measured in the chicken as an estimate of its capacity to synthesize fatty acids (FAs) de novo when fed a biguanide. Malic enzyme (ME) activity was monitored because it provides reducing equivalents (nicotinamide adenine dinucleotide phosphate [NADPH]) for the synthesis of FAs. Isocitrate: NADP+ oxidoreductase-[decarboxylating] (ICD) may both function as a residual source for the provision of NADPH and provide a coreactant for transamination. Aspartate aminotransferase (AAT) aids in the removal of excess amine groups formed during periods of protein degradation or inhibition of lipogenesis.

2. Methods and materials

2.1. Animals and diets

We formulated diets that were slightly low in crude protein (18%) containing 0, 0.25, 0.5, and 1 g of MET per kilogram (experiment 1). Chickens were placed on these diets at 7 days of age and allowed to grow for 21 days. In the second experiment, we followed the above