Aldosterone deficiency in mice burdens respiration and accentuates diet-induced hyperinsulinemia and obesity

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Aldosterone synthase inhibitors (ASIs) should alleviate obesity-related cardiovascular and renal problems resulting partly from aldosterone excess, but their clinical use may have limitations. To improve knowledge for the use of ASIs, we investigated physiology in aldosterone synthase-knockout (ASKO) mice. On regular chow diet (CD), ASKO mice ate more and weighed less than WT mice, largely because they hyperventilated to eliminate acid as CO2. Replacing CD with high-fat diet (HFD) lessened the respiratory burden in ASKO mice, as did 12- to 15-hour fasting. The latter eliminated the genotype differences in respiratory workload and energy expenditure (EE). Thus, aldosterone deficiency burdened the organism more when the animals ate carbohydrate-rich chow than when they ate a HFD. Chronic HFD exposure further promoted hyperinsulinemia in ASKO mice that contributed to visceral fat accumulation accompanied by reduced lipolysis, thermogenic reprogramming, and the absence of weight-gain-related EE increases. Intracerebroventricular aldosterone supplementation in ASKO mice attenuated the HFD-induced hyperinsulinemia, but did not affect EE, suggesting that the presence of aldosterone increased the body's energetic efficiency, thus counteracting the EE-increasing effect of low insulin. ASIs may therefore cause acid-overload-induced respiratory burden and promote obesity. Their use in patients with preexisting renal and cardiopulmonary diseases might be contraindicated.
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