Letter to the Editor

11βHSD and the mechanism of gossypol-induced hypokalemia

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Volume 21 of the Journal carried two articles on the contraceptive applications of gossypol (Yu & Chan, 1998; Waites et al., 1998). While Yu & Chan dismissed the risk of hypokalemia as low, Waites et al. reported hypokalemia in up to 10% of men using gossypol. Both reviews agreed that the hypokalemia probably reflects increased renal potassium excretion, but that the mechanism underlying this effect was unknown.

I write to draw attention to an article by Song et al. (1992) which appears to explain the hypokalemia associated with gossypol administration.

In the kidney, potassium excretion is stimulated by aldosterone via type 1 corticosteroid receptors. Although designated as 'mineralocorticoid receptors' (MR), these receptors lack specificity and bind glucocorticoids (cortisol and corticosterone) with equal affinities in vitro. Since glucocorticoid concentrations exceed mineralocorticoid concentrations by over 100-fold in vivo, an intracellular mechanism is required to exclude glucocorticoids from the MR. This takes the form of a high-affinity (type 2) 11β-hydroxysteroid dehydrogenase (11βHSD) which oxidizes glucocorticoids to inert 11-ketosteroid metabolites (Krozowski et al., 1994). In so doing, 11βHSD2 denies glucocorticoids access to corticosteroid receptors, and so selectively allows aldosterone to stimulate sodium/potassium exchange via MR. Hence, if 11βHSD2 is inactivated by mutation, cortisol hyperstimulates the MR, inducing excessive potassium excretion (resulting in hypokalemia) and sodium resorption (leading to endocrine hypertension). This syndrome of 'apparent mineralocorticoid excess' (Ulick et al., 1979) can also result from pharmacological inhibition of 11βHSD. Song et al. (1992) identified gossypol as one of several plant-derived 11βHSD inhibitors. Thus, the hypokalemia associated with gossypol intake can be ascribed to hyperstimulation of potassium excretion following inhibition of cortisol metabolism in the distal nephron of the kidney and colon.

Having offered an explanation for gossypol-induced hypokalemia, one question remains. Why wasn’t hypokalemia reported in a greater proportion of men using gossypol as a contraceptive? Perhaps baseline potassium concentrations and dietary potassium intake can mitigate against the renal impact of inhibiting 11βHSD2 with gossypol.

References


