Effect of Serotonin 4 (5-HT 4) Receptor Agonists on Aldosterone Secretion in Idiopathic Hyperaldosteronism

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ABSTRACT

Serotonin (5-HT) stimulates aldosterone secretion in man through 5-HT$_4$ receptors positively coupled to adenylyl cyclase. In particular, it has been shown that oral administration of a single dose of the 5-HT$_4$ receptor agonist cisapride induces a significant increase in plasma aldosterone levels (PAL) in healthy volunteers. Idiopathic hyperaldosteronism (IH) is a rare disorder characterized by hypertension, hypokalemia and bilateral adrenal hypersecretion of aldosterone. In patients with IH, administration of the 5-HT precursor 5-hydroxytryptophan (5-HTP) is followed by a significant increase in PAL. 5-HTP-induced aldosterone secretion has been attributed to the activation of central serotonergic pathways. The aim of the present study was to evaluate the effect of the oral administration of a single dose of cisapride (10 mg) on aldosterone secretion in 15 patients with IH, in a simple blind fashion *versus* placebo. Cisapride induced a significant increase in PAL but did not affect renin, cortisol and potassium levels. The present study demonstrates that 5-HT$_4$ receptor agonists are able to stimulate aldosterone secretion in patients with IH. These data also indicate that hyperplastic glomerulosa tissue, like normal glomerulosa cells, expresses a functional 5-HT$_4$ receptor. Therefore, 5-HT$_4$ receptor antagonists may represent a new approach in the treatment of primary hyperaldosteronism.

INTRODUCTION

We have previously shown that, in man, serotonin (5-HT) exerts a direct stimulatory effect on adrenocortical cells through activation of 5-HT_4 receptors positively coupled to adenylyl cyclase (1-3). In agreement with these data, we have observed that 5-HT_4 receptor agonists, such as cisapride and zacopride, are able to stimulate aldosterone secretion in healthy volunteers pretreated by dexamethasone (3,4). Idiopathic hyperaldosteronism (IH) is a rare disorder characterized by hypertension, hypokalemia and bilateral adrenal hypersecretion of aldosterone. In patients with IH, it has been shown that oral administration of a single dose of the 5-HT precursor 5-HTP causes a significant increase in plasma aldosterone levels (PAL) but does not affect renin levels which remained suppressed (5). Since 5-HT triggers both CRH neurons (6) and pituitary corticotrophs (7,8), these results raised the question as to whether 5-HT and its precursors act predominantly at the hypothalamic, pituitary or adrenal levels. 5-HT_4 receptor agonists having no influence on ACTH secretion (9), we have investigated, in the present study, the effect of cisapride on aldosterone secretion in patients with IH in order to explore specifically the adrenal sensitivity to 5-HT in this affection.

MATERIALS AND METHODS

15 untreated patients (7 women and 8 men) with newly discovered IH were studied after informed consent and approval of the experimental protocol by the Regional Ethics Committee of Haute-Normandie. The diagnosis of IH was established on the basis of hypertension, hypokalemia, elevated basal PAL, suppressed renin levels in upright position, partial suppression of PAL by sodium loading and absence of adrenal tumor at CT scan. A single dose of cisapride (10 mg) and/or placebo was administered orally to patients at 11 a.m., as previously described (4). Plasma aldosterone, cortisol, renin and potassium were measured in

blood samples taken before and every 30 min during the 3 hours following cisapride or placebo administration. Statistical analysis was performed using Duncan's test after ANOVA.

RESULTS

Cisapride induced a 4-fold increase in PAL ($p < 0.001$, ANOVA) which reached a maximum at 90 min ($p < 0.01$ *vs* t_0 and placebo) and remained elevated during the next 90 min (Fig. 1A). The stimulation of aldosterone secretion by cisapride was observed in all patients (Fig. 1B). In contrast, plasma renin concentration remained suppressed during the study. Similarly, cortisol and potassium levels were not affected by the treatment.

DISCUSSION

5-HT is able to enhance aldosterone production through stimulatory actions on CRH and ACTH secretion involving 5-HT_{1A}, 5-$HT_{2A/2C}$ and 5-HT_3 receptors (6-8). In addition to these indirect effects, *in vivo* and *in vitro* studies have shown that, in man, 5-HT exerts a direct stimulatory effect on zona glomerulosa cells *via* 5-HT_4 receptors positively coupled to adenylyl cyclase (3,4,10). Because of their lack of effect on ACTH secretion, 5-HT_4 receptor agonists are valuable tools to explore *in vivo* the adrenocortical sensitivity to 5-HT (3,4,9). In the present study, we show that the 5-HT_4 receptor agonist cisapride is able to stimulate aldosterone secretion in patients with bilateral zona glomerulosa hyperplasia. The observation that cisapride did not affect cortisol levels confirmed that 5-HT_4 receptor agonists do not stimulate ACTH secretion. In addition, renin and potassium levels were not modified by the treatment indicating that cisapride-evoked stimulation of aldosterone secretion cannot be ascribed to activation of the renin-angiotensin system or elevation of kalemia. These data rather suggest a direct adrenal effect of

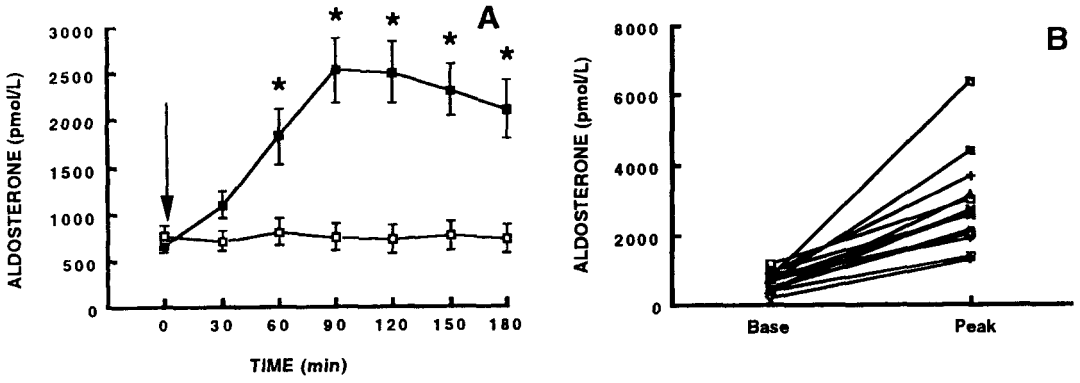

FIGURE 1

A. Effect of cisapride on plasma aldosterone levels in patients with IH. A single dose of cisapride (■) or placebo (□) was administered at t_0 (arrow). * $p < 0.01$ *vs* placebo. B. Basal and maximum plasma aldosterone levels for the 15 patients.

cisapride and strongly support the hypothesis that hyperplastic glomerulosa tissue expresses, like normal glomerulosa cells, a functional 5-HT_4 receptor. 5-HT_4 receptor antagonists may therefore represent a new approach in the treatment of primary hyperaldosteronism.

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