



**HAL**  
open science

## **Effect of Serotonin 4 (5-HT<sub>4</sub>) Receptor Agonists on Aldosterone Secretion in Idiopathic Hyperaldosteronism**

Hervé Lefebvre, Dorthe Cartier, Celine Duparc, Vincent Contesse, Isabelle Lihrmann, Catherine Delarue, Hubert Vaudry, Rodolphe Fischmeister, Jean-Marc Kuhn

► **To cite this version:**

Hervé Lefebvre, Dorthe Cartier, Celine Duparc, Vincent Contesse, Isabelle Lihrmann, et al.. Effect of Serotonin 4 (5-HT<sub>4</sub>) Receptor Agonists on Aldosterone Secretion in Idiopathic Hyperaldosteronism. *Endocrine Research*, 2009, 26 (4), pp.583-587. 10.3109/07435800009048575 . hal-03611671

**HAL Id: hal-03611671**

**https:**

**//hal-universite-paris-saclay.archives-ouvertes.fr/hal-03611671**

Submitted on 23 Mar 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# EFFECT OF SEROTONIN<sub>4</sub> (5-HT<sub>4</sub>) RECEPTOR AGONISTS ON ALDOSTERONE SECRETION IN IDIOPATHIC HYPERALDOSTERONISM

H. Lefebvre <sup>1,2</sup>, D. Cartier <sup>2</sup>, C. Duparc <sup>2</sup>, V. Contesse <sup>2</sup>, I. Lihmann <sup>2</sup>,  
C. Delarue <sup>2</sup>, H. Vaudry <sup>2</sup>, R. Fischmeister <sup>3</sup>, J.M. Kuhn <sup>1,2</sup>

<sup>1</sup>European Institute for Peptide Research (IFRMP 23), Department of Endocrinology and Metabolic Diseases, CHU of Rouen, 76031 Rouen, France  
<sup>2</sup>European Institute for Peptide Research (IFRMP 23), Laboratory of Cellular and Molecular Neuroendocrinology, INSERM U413, UA CNRS, University of Rouen, 76821 Mont-Saint-Aignan, France

<sup>3</sup>ISIT, Laboratory of Cellular and Molecular Cardiology, INSERM U446, University Paris-Sud, Chatenay-Malabry, France

## ABSTRACT

Serotonin (5-HT) stimulates aldosterone secretion in man through 5-HT<sub>4</sub> receptors positively coupled to adenylyl cyclase. In particular, it has been shown that oral administration of a single dose of the 5-HT<sub>4</sub> 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<sub>4</sub> 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<sub>4</sub> receptor. Therefore, 5-HT<sub>4</sub> 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<sub>4</sub> receptors positively coupled to adenylyl cyclase (1-3). In agreement with these data, we have observed that 5-HT<sub>4</sub> 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<sub>4</sub> 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<sub>1A</sub>, 5-HT<sub>2A/2C</sub> and 5-HT<sub>3</sub> 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<sub>4</sub> receptors positively coupled to adenylyl cyclase (3,4,10). Because of their lack of effect on ACTH secretion, 5-HT<sub>4</sub> 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<sub>4</sub> 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<sub>4</sub> 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

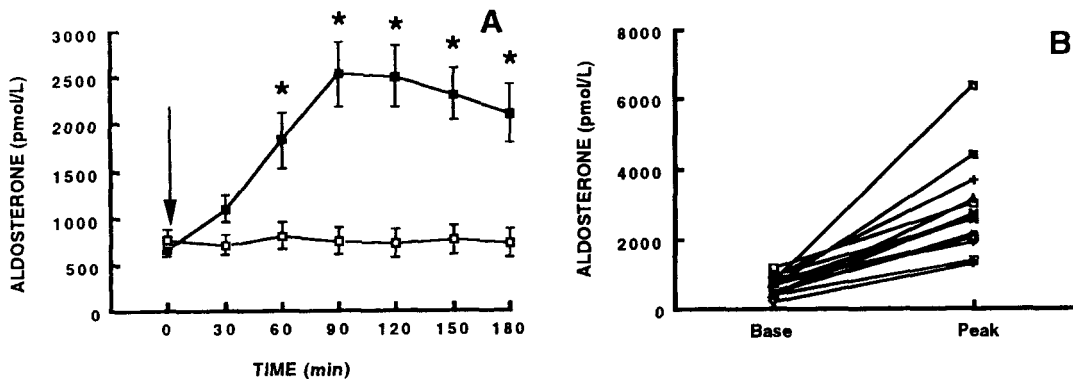


FIGURE 1

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<sub>4</sub> receptor. 5-HT<sub>4</sub> receptor antagonists may therefore represent a new approach in the treatment of primary hyperaldosteronism.

### ACKNOWLEDGEMENTS

This work was supported by a grant from the CHU of Rouen. The authors acknowledge the cooperation of Drs A. Legrand and A. Coquerel with hormonal assays and Dr J.F. Ménard for statistical analysis.

### REFERENCES

1. Lefebvre H, Contesse V, Delarue C, Feuilloley M, Héry F, Grise P, Raynaud G, Verhofstad AAJ, Wolf LM, Vaudry H. 1992 *Neuroscience* 47:999-1007.

2. Lefebvre H, Contesse V, Delarue C, Soubrane C, Legrand A, Kuhn JM, Wolf LM, Vaudry H. 1993 *J Clin Endocrinol Metab* 77:1662-1666.
3. Lefebvre H, Contesse V, Delarue C, Vaudry H, Kuhn JM. 1998 *Horm Metab Res* 30:1-6.
4. Lefebvre H, Contesse V, Delarue C, Legrand A, Kuhn JM, Vaudry H, Wolf LM. 1995 *J Clin Endocrinol Metab* 80:504-507.
5. Shenker Y, Gross MD, Grekin RJ. 1985 *J Clin Invest* 76:1485-1490.
6. Calogero AE, Bernardini R, Margioris AN, Bagdy G, Gallucci WT, Munson PJ, Tamarkin L, Tomai TP, Brady L, Gold PW, Chrousos GP. 1989 *Peptides* 10:189-200.
7. Spinedi E, Negro-Vilar A. 1983 *Endocrinology* 112:1217-1223.
8. Calogero AE, Bagdy G, Burrello N, Polosa P, D'Agata R. 1995 *Eur J Endocrinol* 133:251-254.
9. Lefebvre H, Contesse V, Delarue C, Kuhn JM, Vaudry H, Wolf LM. 1996 *Eur J Clin Pharmacol* 51:49-51.
10. Contesse V, Lefebvre H, Lenglet S, Kuhn JM, Delarue C, Vaudry H. 2000 *Can J Physiol Pharmacol* in press.