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Review

Paracrine control of steroidogenesis by serotonin in adrenocortical neoplasms

H. Lefebvre [a,b,*], C. Duparc [a], G. Prévost [a,b], M.C. Zennaro [c], J. Bertherat [d], E. Louiset [a]

[a] INSERM, U982, Laboratory of Differentiation & Neuronal and Neuroendocrine Communication, IRIB, University of Rouen, Mont-Saint-Aignan, France
[b] Department of Endocrinology, University Hospital of Rouen, Rouen, France
[c] INSERM, UMRS 970, Paris Cardiovascular Research Center, Paris, France
[d] Department of Endocrinology, University Hospital Cochin and Cochin Institute, Assistance Publique-Hôpitaux de Paris, Université Paris V, Paris, France

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ABSTRACT

Serotonin (5-hydroxytryptamine; 5-HT) is able to activate the hypothalamo–pituitary–adrenal axis *via* multiple actions at different levels. In the human adrenal gland, 5-HT, released by subcapsular mast cells, stimulates corticosteroid production through a paracrine mode of communication which involves 5-HT receptor type 4 (5-HT_4) primarily located in zona glomerulosa. As a result, 5-HT is much more efficient to stimulate aldosterone secretion than cortisol release *in vitro* and administration of 5-HT_4 receptor agonists to healthy individuals is followed by an increase in plasma aldosterone levels without any change in plasma cortisol concentrations. Interestingly, adrenocortical hyperplasias and tumors responsible for corticosteroid hypersecretion exhibit various cellular and molecular defects which tend to reinforce the intraadrenal serotonergic tone. These pathophysiological mechanisms, which are summarized in the present review, include an increase in adrenal 5-HT production and overexpression of 5-HT receptors in adrenal neoplastic tissues. Altogether, these data support the concept of adrenal serotonergic paracrinopathy and suggest that 5-HT and its receptors may constitute valuable targets for pharmacological treatments of primary adrenal diseases.

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1. Introduction

In mammals, serotonin (5-hydroxytryptamine, 5-HT) regulates the adrenocortical function through multiple effects at different levels of the hypothalamic–pituitary–adrenal (HPA) axis. In fact, 5-HT both triggers corticotropin-releasing hormone (CRH) release from hypothalamic neurons and stimulates corticotropin (ACTH) secretion from pituitary corticotrophs (Chen and Miller, 2012; Jørgensen et al., 2002). The serotonergic control of the corticotropic function seems to play an important role in the physiology of the HPA axis (Contesse et al., 2000; Jørgensen, 2007). In particular, several observations have shown that central serotonergic pathways are involved in the circadian periodicity of ACTH production and the activation of HPA in response to stress (Chen and Miller, 2012). The receptor types

Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; 5-HT_4, 5-HT receptor type 4; HPA, hypothalamic–pituitary–adrenal; ACTH, adrenocorticotropic hormone, corticotropin; CRH, corticotropin-releasing hormone; MC, mast cells; SCF, stem cell factor; PPNAD, primary pigmented nodular adrenocortical disease; *PRKAR1A*, PKA regulatory unit 1α; BMAH, bilateral macronodular adrenal hyperplasia; PKA, protein kinase A; GPCR, G-protein coupled receptor.

* Corresponding author. INSERM U982, Laboratory of Differentiation & Neuronal and Neuroendocrine Communication, IRIB, Department of Endocrinology, Hospital of Boisguillaume, CHU of Rouen, 76031 Rouen cedex, France. Tel.: +33 232 88 90 81; fax: +33 232 88 91 54.
E-mail address: herve.lefebvre@chu-rouen.fr (H. Lefebvre).

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involved in the control of ACTH secretion by 5-HT may vary among mammalian species. In rat, they belong to the 5-$HT_{1A/1B}$, 5-$HT_{2A/2C}$ and 5-HT_3 subtypes but it is not excluded that other receptor types, such as 5-HT_4, 5-HT_5 and 5-HT_7 receptors, may partly mediate the ACTH response to 5-HT (Calogero et al., 1995; Jørgensen, 2007; Saphier et al., 1995). Few data are available on the regulation of the corticotropic function by 5-HT in man. The action of 5-HT on the hypothalamic–pituitary complex may involve the 5-HT_1 and 5-HT_2 receptors (Schüle, 2007).

5-HT is also able to activate the renin angiotensin system which is a major regulator of aldosterone secretion. Clinical trials have shown an increase in plasma renin activity after administration of 5-HT precursors, 5-HT itself or 5-HT reuptake inhibitors to healthy volunteers and/or depressed patients (Ahmed et al., 2011; Mantero et al., 1982; Modlinger et al., 1979). The receptors that mediate the effect of 5-HT on renin production by the juxta-glomerular apparatus are not known in man. They seem to belong to the 5-HT_{1B} and 5-$HT_{2A/2C}$ types in rat (Rittenhouse et al., 1994).

In addition to its indirect actions on corticosteroid production *via* ACTH and renin secretions, 5-HT is also able to directly activate the secretory activity of the adrenal cortex through a paracrine mechanism (Contesse et al., 2000). In the human adrenal gland, 5-HT is synthesized by perivascular mast cells (MC) primarily located in the subcapsular region of the cortex (Fig. 1 A and B) (Lefebvre et al., 1992, 2001). The regulation of 5-HT secretion in the adrenal tissue is not known but the observation that adrenal MC establish connections with cortical nerve endings suggests that 5-HT may be produced in response to activation of the sympathetic system (Duparc et al., 2012). After its release, 5-HT stimulates corticosteroid secretion through activation of 5-HT_4 receptors positively coupled with adenylyl cyclase and calcium influx (Contesse et al., 2000). Interestingly, 5-HT more efficiently stimulates aldosterone than cortisol secretion *in vitro* (Contesse et al., 2000; Lefebvre et al., 2001). This finding is consistent with other observations indicating that the 5-HT_4 receptor is primarily expressed in zona glomerulosa cells at both mRNA and protein levels (Cartier et al., 2005) (Fig. 1C). It is also conceivable that adrenal 5-HT may locally activate steroid production through indirect mechanisms involving modulation of adrenal blood flow and/or production of cytokines by adrenocortical cells, as shown in rat (Hinson et al., 1991; Ritchie et al., 1996). Like the central nervous system and other peripheral organs, the human adrenal gland is capable of metabolizing 5-HT into inactive compounds such as 5-hydroxyindolacetic acid (5-HIAA) and 5-hydroxytryptophol (Lefebvre et al., 1992, 2001). This process, which is thought to be aimed at avoiding overstimulation of steroid production by the indolamine, involves monoamine oxidase type A which is principally expressed by chromaffin cells (Lefebvre et al., 2001).

Consistently with these data obtained *in vitro, in vivo* studies have shown that 5-HT_4 receptor agonists, like metoclopramide (Carey et al., 1980), zacopride (Lefebvre et al., 1993), cisapride (Lefebvre et al., 1995), mosapride (Gale et al., 2004) and tegaserod (Lampron et al., 2009), stimulate aldosterone secretion but have no influence on plasma cortisol concentrations in healthy volunteers. Renin and ACTH productions were not modified by these compounds indicating that the aldosterone response resulted from direct activation of adrenal 5-HT_4 receptors, as previously shown *in vitro*. Interestingly, the stimulatory action of 5-HT_4 receptor agonists on aldosterone production was found to be additive to that of angiotensin II in normal individuals (Lefebvre et al., 1995) and sustained pharmacological (and thus supraphysiological) activation of adrenal 5-HT_4 receptors led to rapid desensitization of the aldosterone response (Lefebvre et al., 1998).

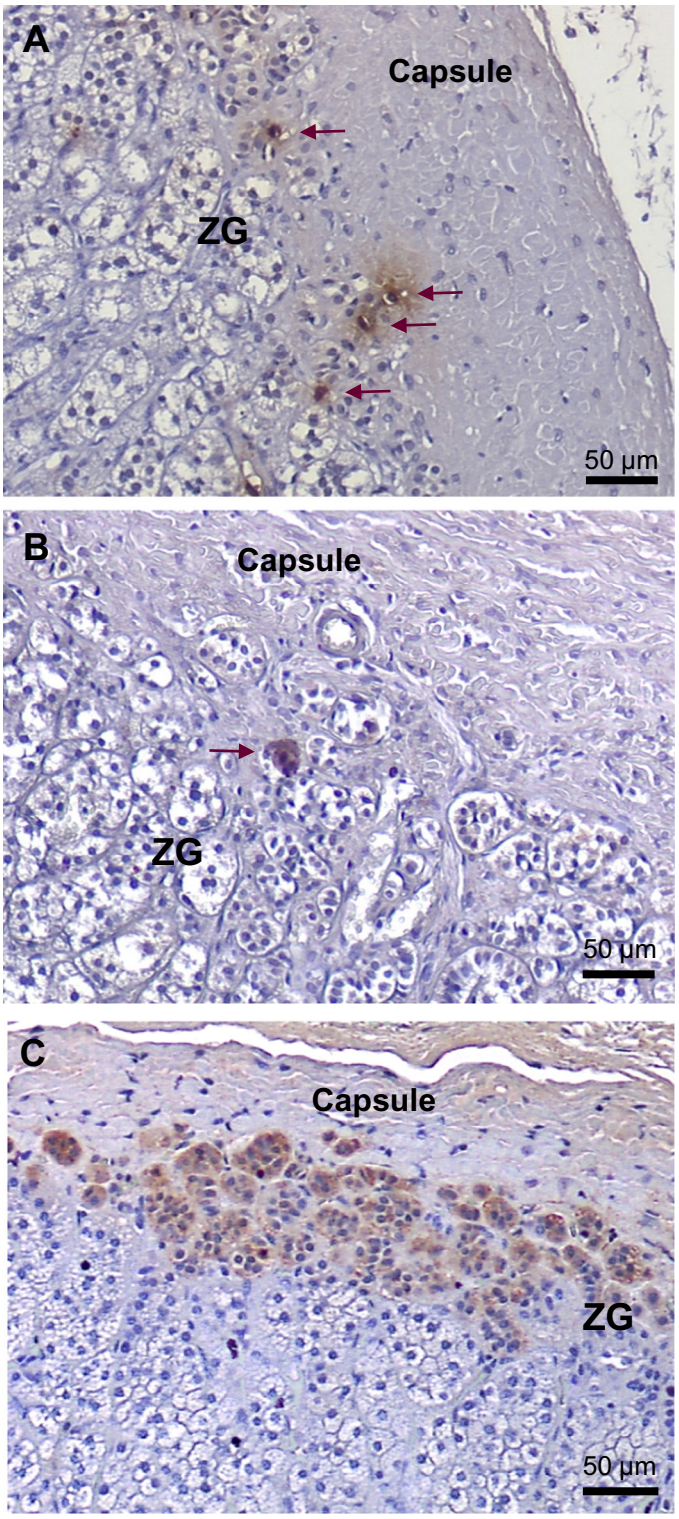

Fig. 1. Localization of mast cells, the 5-HT synthesizing enzyme tryptophan hydroxylase and 5-HT_4 receptors in the normal adrenal cortex. (A) Tryptase-immunopositive mast cells (arrows) were observed in the subcapsular region of the adrenal cortex, close to zona glomerulosa (ZG) cells. (B) Tryptophan hydroxylase immunoreactivity was exclusively detected in mast cells (arrow) while (C) zona glomerulosa is diffusely stained by 5-HT_4 receptor antibodies.

2. Sources of 5-HT in steroid-producing adrenocortical hyperplasias and tumors

Several observations indicate that intraadrenal production of 5-HT may be enhanced in adrenocortical hyperplasias and tumors responsible for steroid excess. First, an increase in mast cell density is noticed in aldosterone-producing adenoma (APA) tissues in comparison with normal adrenals (Duparc et al., 2012). Mast cell proliferation appears to be the consequence of overexpression of