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SEROTONINERGIC STIMULATION OF ALDOSTERONE SECRETION *IN VIVO*: ROLE OF THE HYPOTHALAMO–PITUITARY ADRENAL AXIS

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Summary—The control of aldosterone secretion *in vivo* by serotonin was studied in conscious rats. Serial blood samples were taken from indwelling arterial cannulae before and after i.p. administration of 1 ml (4g/l) 5-hydroxytryptophan (5-HTP), the precursor of serotonin (5-HT), or saline, and analysed for 5-HTP, serotonin, 5-hydroxyindoleacetic acid, plasma renin activity (PRA), corticosterone, aldosterone, sodium and potassium concentration. The relative contribution of the hypothalamo–pituitary adrenal axis was investigated in animals pretreated with the synthetic glucocorticoid dexamethasone. 5-HTP caused a significant increase in all parameters within 45 min except for plasma sodium and potassium. Saline administration showed no significant effect. Dexamethasone pretreatment significantly impaired the corticosterone and aldosterone response to 5-HTP, although the aldosterone response was merely attenuated. No other parameter was affected by dexamethasone pretreatment. The results show that administration of 5-HTP, which increases serum serotonin levels, stimulates PRA, corticosterone and aldosterone secretion. Dexamethasone pretreatment inhibits the aldosterone response, though not completely, suggesting that the stimulatory action of 5-HTP involves the release of ACTH, which stimulates corticosterone and aldosterone secretion by the adrenal cortex. The failure of dexamethasone to block the aldosterone response completely, suggests the involvement of other mechanisms such as the renin–angiotensin system or a direct action of serotonin on the adrenal zona glomerulosa.

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) stimulates aldosterone secretion *in vitro* [1, 2]. However, its physiological relevance in the control of the secretion of the mineralocorticoid remains unclear. Some groups have shown that infusions of serotonin in man increase aldosterone secretion, without any change in plasma cortisol [3]. In contrast, other studies have shown that administration of tryptophan or 5-hydroxytryptophan (5-HTP), the immediate precursors of serotonin, not only increase circulating levels of aldosterone but also ACTH and cortisol, suggesting that steroidogenesis may be centrally mediated by stimulation of the hypothalamus and pituitary gland [4–6].

In order to establish a role for the hypothalamo–pituitary axis in serotonin-stimulated aldosterone secretion, we have monitored the effects of 5-HTP administration to rats, prior to and after pretreatment with the synthetic glucocorticoid dexamethasone. Serum 5-HTP, serotonin, its metabolism to 5-hydroxyindoleacetic acid (5-HIAA), plasma renin activity (PRA), corticosterone, aldosterone, sodium and potassium levels and arterial blood pressure were then measured over a given time course. The experimental model used was the conscious rat with an indwelling carotid arterial cannula. This allowed blood samples to be taken under minimal stress and without anaesthesia, as well as direct monitoring of arterial blood pressure.

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EXPERIMENTAL

Materials

Hypnorm was from Janssen Pharmaceuticals (Oxford, England). Hypnovel was from Roche Pharmaceuticals (Herts., England). Heparin was from Leo Laboratories (Bucks., England). Serotonin (creatinine sulphate complex), 5-HTP, 5-HIAA, thrombin, pargyline and chlorimipramine were from Sigma Chemical Co. Ltd (Dorset, England). Dexamethasone was from Organon Labs (Cambridge, England).

For the high pressure liquid chromatography (HPLC) analysis, ethylenediaminetetraacetic acid (EDTA) was from BDH (Dorset, England). Perchloric acid was from May and Baker (Manchester, England). *N*-methyl-serotonin was from Aldridge Chemical Co. (Kent, England). HPLC grade water and methanol were from Rathburn Chemicals (Lothian, Scotland). Aldosterone antisera was a gift from Dr F. A. O. Mendelsohn, Australia. All other antisera and radiolabels were produced in our laboratories according to previously published methods [7–10].

Cannulation

Male Wistar rats (250–300 g) were anaesthetised by i.p injection of Hypnorm (0.5 ml/kg) and Hypnovel (0.5 ml/kg). The carotid artery was cannulated and the free end of the cannula threaded through to the back of the animals' neck using a trochar, where it was tied in position and kept closed by means of a small metal pin in the free end. The trochar was removed and the neck wound closed using metal clips. Immediately following surgery the cannulae were flushed with 20 μl undiluted heparin (5000 U/ml) and then daily with 20 μl undiluted heparin. The animals were allowed a 2 day post-operative recovery period before any experimental work commenced. The cannulae were used as a route of blood sampling throughout the experimental procedure. Three groups of animals were used ($n = 4$/group). Two of the groups of animals were pretreated with 15 μg dexamethasone in 1 ml saline at 17:30 h on the day prior to and at 09:00 h on the morning of the experiment. Dexamethasone was given i.p. The third untreated group was given 1 ml saline i.p.

Experimental procedure

All the experiments commenced at 09:30 h. A basal blood sample (time = 0) was taken via the cannulae from all the animals immediately before i.p. administration of 1 ml 5-HTP (4 g/l) or 1 ml of saline (0.9% w/v), depending on the group. Further blood samples were taken at 45 min intervals thereafter. A total of four blood samples including the basal were taken on the day of the experiment in addition to a 24 h sample taken the following day. The cannulae were flushed immediately after drawing blood with 30 μl heparin diluted 1:20 in saline. Only 250 μl of blood was drawn off at each time point to minimize volume depletion. Blood (225 μl) was transferred to a tube containing 25 μl of ice cold EDTA (27 mmol/l). This was mixed thoroughly and centrifuged at 10,000 *g* for 15 min. The plasma was removed and stored at −20°C until measurement of PRA, corticosterone and aldosterone by radioimmunoassay (RIA) [7–10]. Sodium and potassium were measured by flame photometry at the Royal Hospital for Sick Children, Edinburgh, Scotland. 20 μl of the remaining whole blood were added to 180 μl of a cocktail containing thrombin (1100 U/l), chlorimipramine (1.1 μmol/l) and pargyline (11.1 μmol/l) This was left at 4°C for at least 2 h to allow complete release of serotonin by the platelets, and then centrifuged at 10,000 *g* for 15 min. The supernatant was removed and stored at −20°C before estimation of 5-HTP, serotonin and 5-HIAA by HPLC [11].

Statistical analysis

Results are illustrated as mean ± standard error of the mean (SEM). Statistical significance between separate groups at the same time point was calculated using Student's *t*-test for unpaired samples. Significance between different time points in the same group of animals was estimated using Student's *t*-test for paired samples. A P value of <0.05 was considered significant.

RESULTS

Serum 5-HTP concentration in each of the three groups throughout the experimental time course is shown in Fig. 1(A). Basal 5-HTP levels in the dexamethasone pretreated groups were not significantly different from the untreated group. Following 5-HTP administration, 5-HTP levels increased maximally at 45 min from 2.1 ± 0.9 to 16.9 ± 1.7 μmol/l ($P < 0.001$) in the dexamethasone pretreated group and from 1.4 ± 0.1 to 21.9 ± 0.8 μmol/l ($P < 0.001$) in the untreated group. Both returned to basal values within 135 min. Comparison of the increases observed at 45 min revealed that dexamethasone pretreatment had no significant effect on 5-HTP uptake following its administration. Administration of saline to untreated (data not shown) or dexamethasone pretreated animals showed no significant effect on 5-HTP levels.

Serum serotonin concentration in each of the three groups throughout the experimental time course is shown in Fig. 1(B). Basal sero-

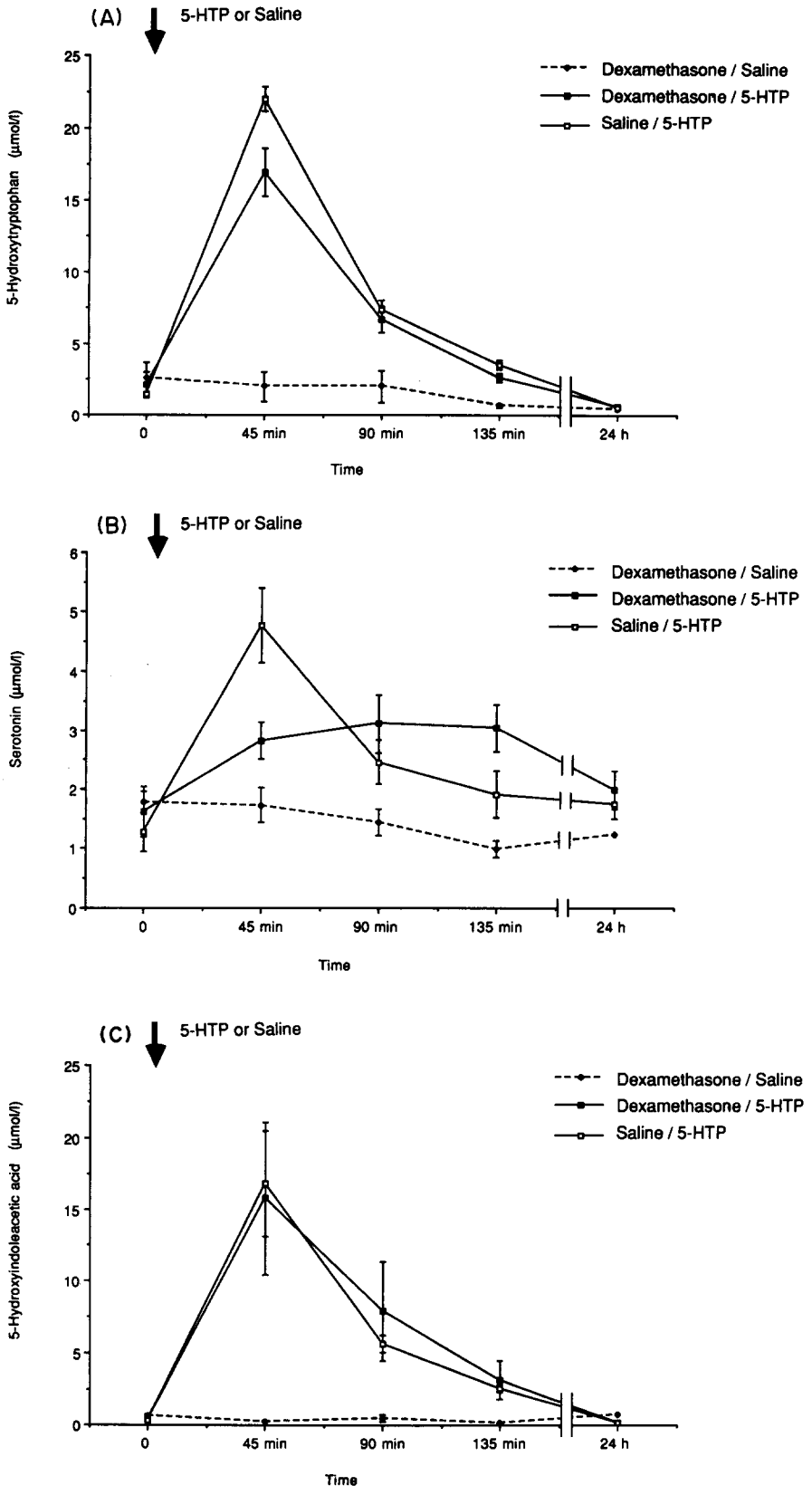

Fig. 1. The effect of 5-HTP or saline administration, given immediately after the collection of the basal blood sample (time = 0), on (A) serum 5-HTP concentration (B) serum serotonin concentration and (C) serum 5-HIAA concentration, in untreated animals and those pretreated with dexamethasone ($n = 4$/group).

tonin levels in the dexamethasone pretreated groups were not significantly different from the untreated group. Following 5-HTP administration, serotonin levels increased maximally from 1.6 ± 0.4 to $3.1 \pm 0.5\,\mu$mol/l ($P < 0.05$) at 90 min in the dexamethasone pretreated group and from 1.3 ± 0.3 to $4.8 \pm 0.6\,\mu$mol/l ($P < 0.01$) at 45 min in the untreated group. Both returned to basal values within 24 h. Although there was no significant difference in the maximum levels of serotonin following 5-HTP administration, the time course of the increase was altered. However, comparison of the increases observed at 45 min in each group showed no significant difference. Administration of saline to untreated (data not shown) or dexamethasone pretreated animals showed no significant effect on serotonin levels.

Serum 5-HIAA concentration in each of the three groups throughout the experimental time course is shown in Fig. 1(C). Basal 5-HIAA levels in the dexamethasone pretreated groups were not significantly different from the untreated group. Following 5-HTP administration, 5-HIAA levels increased maximally at 45 min from 0.3 ± 0.05 to $15.8 \pm 5.3\,\mu$mol/l ($P < 0.01$) in the dexamethasone pretreated group and from 0.3 ± 0.04 to $16.8 \pm 3.7\,\mu$mol/l ($P < 0.05$) in the untreated group. Both returned to basal values within 24 h. Comparison of the increases observed at 45 min revealed that dexamethasone had no significant effect on the formation of 5-HIAA following administration of 5-HTP. Administration of saline to untreated (data not shown) or dexamethasone pretreated animals showed no significant effect on 5-HIAA levels.

PRA in each of the three groups throughout the experimental time course is shown in Fig. 2. Basal PRA in the dexamethasone pretreated groups were not significantly different from the untreated group. Following 5-HTP administration, PRA increased maximally at 45 min from 1.2 ± 0.5 to $27.6 \pm 15.4\,\mu$g/l/h ($P < 0.05$) in the dexamethasone pretreated group and from 0.9 ± 0.2 to $44.3 \pm 12.8\,\mu$g/l/h ($P < 0.05$) in the untreated group. Both returned to basal values within 135 min. Comparison of the increases observed at 45 min revealed that dexamethasone had no significant effect on PRA following administration of 5-HTP. Administration of saline to untreated (data not shown) or dexamethasone pretreated animals showed no significant effect on PRA.

Plasma corticosterone concentration in each of the three groups throughout the experimental time course is shown in Fig. 3. Basal corticosterone levels in the dexamethasone pretreated groups were 20.5 ± 12.9 and 41.9 ± 38.7 nmol/l compared with 99.4 ± 28.7 nmol/l in the untreated group. Following 5-HTP administration, corticosterone levels increased maximally to 762.5 ± 147.4 nmol/l ($P < 0.01$) at 45 min in the untreated group and returned to basal values within 90 min. There was no significant increase in corticosterone in the dexamethasone pretreated group following 5-HTP administration. Comparison of the levels of cortico-

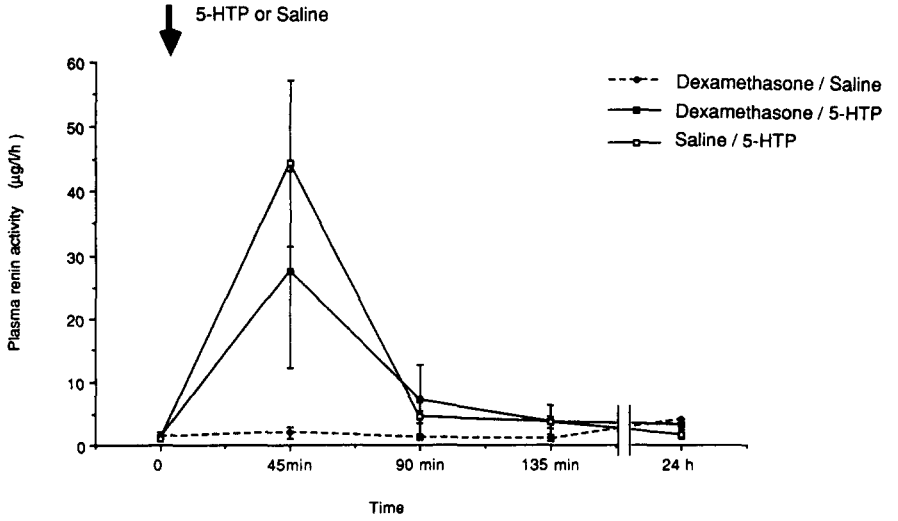

Fig. 2. The effect of 5-HTP or saline administration, given immediately after the collection of the basal blood sample (time = 0), on PRA in untreated animals and those pretreated with dexamethasone ($n = 4$/group).

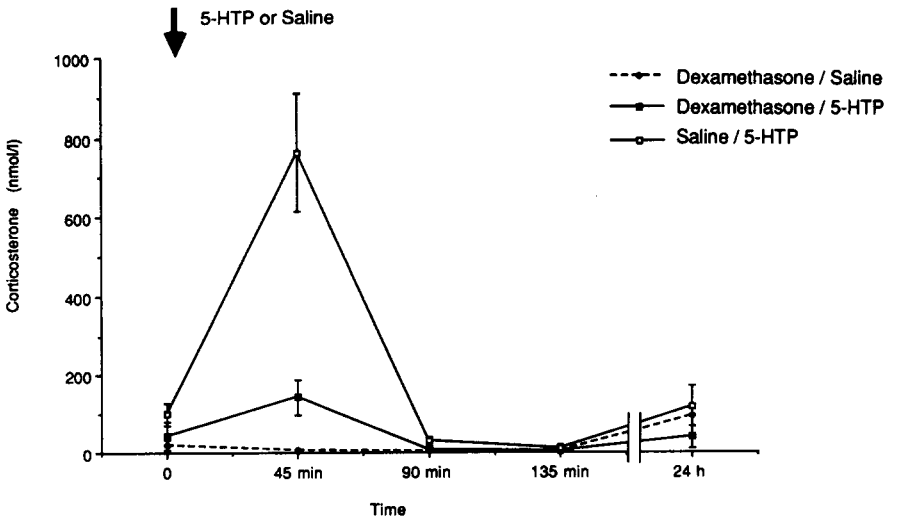

Fig. 3. The effect of 5-HTP or saline administration, given immediately after the collection of the basal blood sample (time = 0), on plasma corticosterone concentration in untreated animals and those pretreated with dexamethasone ($n = 4$/group).

sterone at 45 min in the 5-HTP treated groups revealed that dexamethasone pretreatment significantly inhibited the formation of corticosterone following administration of 5-HTP ($P < 0.01$). Administration of saline to untreated (data not shown) or dexamethasone pretreated animals showed no significant effect on corticosterone levels.

Plasma aldosterone concentration in each of the three groups throughout the experimental time course is shown in Fig. 4. Basal aldosterone levels in the dexamethasone pretreated groups were not significantly different from the untreated group. Following 5-HTP administration, aldosterone levels increased maximally at 45 min from 0.25 ± 0.05 to 0.50 ± 0.01 nmol/l ($P < 0.01$) in the dexamethasone pretreated group and from 0.24 ± 0.01 to 1.42 ± 0.21 nmol/l ($P < 0.001$) in the untreated group. Both returned to basal values within 135 min. Comparison of the increases observed at 45 min revealed that dexamethasone pretreatment significantly inhibited aldosterone secretion following administration of 5-HTP ($P < 0.01$), though not completely. Administration of saline to untreated (data not shown) or dexamethasone pretreated animals showed no significant effect on aldosterone levels.

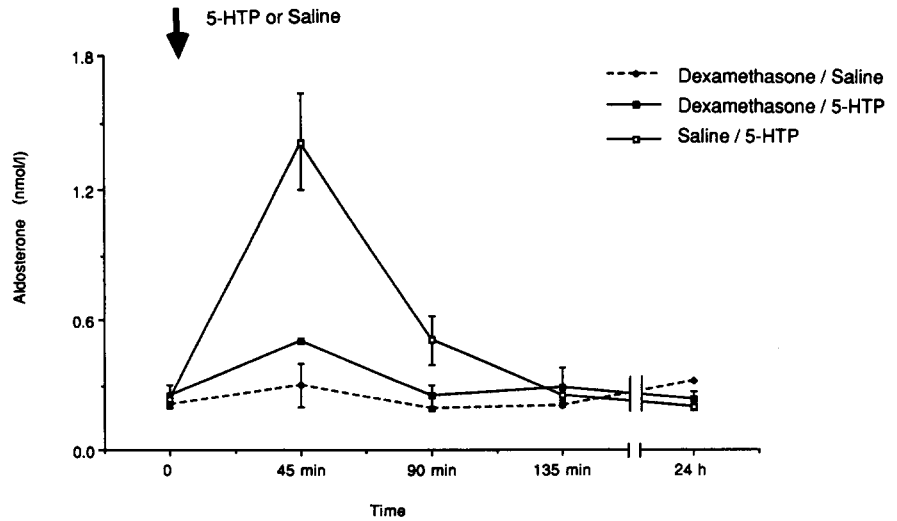

Fig. 4. The effect of 5-HTP or saline administration, given immediately after the collection of the basal blood sample (time = 0), on plasma aldosterone concentration in untreated animals and those pretreated with dexamethasone ($n = 4$/group).

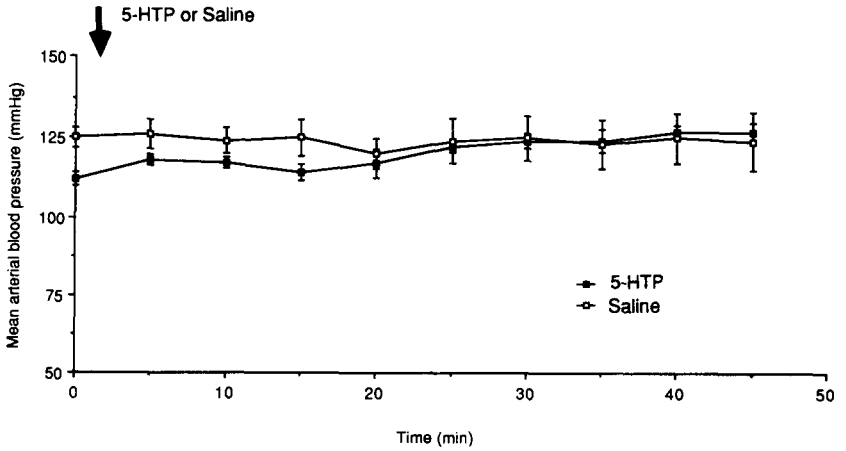

Fig. 5. The effect of 5-HTP or saline administration, given immediately after time = 0, on mean arterial blood pressure (mmHg), which was monitored every 5 min for a total of 45 min, by a pressure transducer coupled to the arterial cannula ($n = 4$/group).

The effect of saline or 5-HTP administration on mean arterial blood pressure (MABP) is shown in Fig. 5. MABP was monitored at time = 0, before administration of 5-HTP or saline, and every 5 min thereafter for 45 min. Comparison of basal values in the two groups revealed a significant ($P < 0.05$) difference in MABP, which was 112 ± 2 mmHg in the 5-HTP treated group and 125 ± 3 mmHg in the saline treated group. Administration of 5-HTP caused a significant increase in MABP from 112 ± 2 to 122 ± 2 ($P < 0.01$), 124 ± 2 ($P < 0.01$), 124 ± 4 ($P < 0.05$), 127 ± 2 ($P < 0.01$) and 127 ± 3 mmHg ($P < 0.01$) at 25, 30, 35, 40 and 45 min, respectively. Saline administration caused no significant change in MABP.

Plasma sodium and potassium were measured in this study but showed no significant change on administration of either 5-HTP or saline (data not shown).

DISCUSSION

The control of aldosterone secretion *in vivo* by serotonin was studied in conscious rats with indwelling arterial cannulae, a technique designed to enable the easy withdrawal of blood without the use of an anaesthetic which would activate the renin–angiotensin system. Serial blood samples were taken under minimal stress conditions via the cannulae, before and after administration of either saline or the serotonin precursor, 5-HTP. To assess the role of the hypothalamo–pituitary adrenal axis in the action of serotonin, the study was repeated in animals following pharmacological blockade of ACTH secretion using the synthetic glucocorticoid dexamethasone.

In the group of animals receiving no pretreatment, the results show that 5-HTP administration increased serum levels of 5-HTP, 5-HIAA and to a lesser degree serotonin. Some groups have failed to show an increase in serotonin following 5-HTP treatment [5] and this may be due to the time-course of blood sampling and the fact that serotonin was measured in plasma rather than serum. The inconsistency between the magnitude of the increase in serum serotonin and that of its precursor and metabolite may be explained in a number of ways. Firstly, basal serum levels of 5-HTP and 5-HIAA are relatively low, whereas serum serotonin levels are high due to the fact that platelets store serotonin. Therefore, the increase in serotonin is being measured against high endogenous levels, whilst the increase in 5-HTP and 5-HIAA are measured against relatively low serum levels. Secondly, serotonin may be taken up into extra-circulatory storage sites such as the gut and the adrenal gland, and this would remain undetected in serum estimations. Thirdly, the conversion of 5-HTP to serotonin may take place predominantly within the central nervous system (CNS) as 5-HTP can cross the blood–brain barrier, and this would also remain undetected in serum. Finally, serotonin may be rapidly metabolized to 5-HIAA.

In addition to the changes in 5-HTP, serotonin and 5-HIAA concentration, 5-HTP administration also caused significant increases in PRA, corticosterone and aldosterone. Similar increases in aldosterone secretion have been

shown by other groups following administration of 5-HTP, serotonin or tryptophan, but conflicting results have been reported for PRA and ACTH [3–6, 12]. No change in potassium or sodium levels, which may account for the increase in aldosterone secretion, were observed in this or the aforementioned studies by other groups. The control group of animals which received saline rather than 5-HTP showed no significant change in any parameter, indicating that stress induced by the injection or animal handling was not responsible for the results in the 5-HTP treated group.

Although 5-HTP administration stimulates aldosterone secretion *in vivo*, it is unclear how this effect is mediated. The results however suggest a number of possibilities. Firstly, 5-HTP may be converted to serotonin either centrally, peripherally or indeed locally, and act on specific serotonin receptors in the zona glomerulosa to stimulate corticosterone and aldosterone secretion, as has previously been reported in isolated cells and in the isolated perfused adrenal gland [1, 2, 13]. The metabolism of serotonin to 5-HIAA and another unidentified metabolite by adrenal capsular tissue is well known [14], and recent unpublished observations in our laboratory have indicated the presence of L-aromatic amino acid decarboxylase, the enzyme which converts 5-HTP to serotonin. Secondly, the increase in PRA and previous studies by our group using the angiotensin converting enzyme inhibitor captopril suggest that the renin–angiotensin system may be important in serotonin-stimulated aldosterone secretion [15]. Serotonin may increase renin release directly via serotoninergic neurones [12] or indirectly by decreasing blood pressure, although conflicting results have been reported regarding the effect of serotonin or 5-HTP on blood pressure [3, 5, 16]. To resolve this question, the blood pressure of the animals was measured prior to and following administration of either saline or 5-HTP. No significant decrease in blood pressure was observed in either group. It therefore seems unlikely that the increase in PRA is mediated by a decrease in blood pressure. There was however a small but significant increase in blood pressure in the group of animals receiving 5-HTP and it is possible that this is secondary to activation of the renin–angiotensin system.

The third theory relating to the mechanism of action of 5-HTP is that serotonin formed within the CNS may act on the hypothalamus and/or pituitary to stimulate the release of corticotropin releasing factor (CRF) and ACTH, respectively, as has been previously shown in different experimental models by a number of other groups [17–19]. The release of ACTH and other pituitary derived peptides such as α-MSH would stimulate secretion of corticosterone and aldosterone from the adrenal cortex. This theory is supported by the significant increase in corticosterone secretion observed following 5-HTP administration. The central action of 5-HTP was investigated further by conducting experiments similar to the initial studies, with the exception that the animals were pretreated with dexamethasone, a synthetic glucocorticoid which inhibits ACTH release from the pituitary gland. Successful suppression of ACTH secretion by dexamethasone was monitored by the decrease in basal corticosterone concentration and also by the complete failure of 5-HTP to increase corticosterone levels. The results show that dexamethasone pretreatment did not impair the uptake of 5-HTP or its subsequent conversion to serotonin and 5-HIAA. Similarly, the PRA response to 5-HTP was unaffected. However, the increases in both corticosterone and aldosterone were significantly inhibited, although the aldosterone response was not completely suppressed. The inhibition of 5-HTP stimulated aldosterone secretion by dexamethasone suggests that the action of serotonin on adrenal function in this model may be mediated, at least in part, by activation of the hypothalamo–pituitary adrenal axis, resulting in the release of ACTH which stimulates corticosterone and aldosterone secretion from the adrenal cortex. Alternatively, ACTH may be required permissively for the steroidogenic action of serotonin. Centrally mediated effects of serotonin on steroidogenesis have been suggested by a number of groups who have shown that blockade of the peripheral conversion of 5-HTP to serotonin with carbidopa, therefore allowing elevation of serotonin exclusively within the CNS, enhanced the aldosterone response to 5-HTP [20]. However, carbidopa also blocks the formation of dopamine which inhibits aldosterone secretion. Therefore, the enhancement of aldosterone may be due to dopamine removal rather than to a centrally mediated action of serotonin. For this reason carbidopa was not utilized in any of these studies.

In summary, the results of this study show that administration of 5-HTP, which increases

circulating levels of serotonin, activates the hypothalamo–pituitary adrenal axis. However, the failure of dexamethasone to completely inhibit the aldosterone response to 5-HTP, even although corticosterone secretion was completely suppressed, suggests that another mechanism is also operative. This may be a direct action of serotonin on the adrenal cortex and/or an indirect effect via activation of the renin–angiotensin system, as suggested by the increase in PRA following 5-HTP administration. It is almost certain that the full steroidogenic response to 5-HTP involves a complex interaction between the CNS, the renin–angiotensin system and perhaps a direct effect of serotonin on the zona glomerulosa. Any alterations in this fine equilibrium may result in altered adrenal responsiveness leading to changes in mineralocorticoid secretion.

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REFERENCES

1. Müller J. and Ziegler W. H.: Stimulation of aldosterone biosynthesis *in vitro* by serotonin. *Acta Endocr. (Copenh).* **59** (1968) 23–35.
2. Haning R., Tait S. A. S. and Tait J. F.: *In vitro* effects of ACTH, angiotensins, serotonin and potassium on steroid output and conversion of corticosterone to aldosterone by isolated cells. *Endocrinology* **87** (1970) 1147–1167.
3. Mantero F., Opocher G., Boscaro M. and Armanini D.: Effect of serotonin on plasma aldosterone in man. *J. Endocr. Invest.* **5** (1982) 97–99.
4. Modlinger R. S., Schonmuller J. M. and Arora S. P.: Stimulation of aldosterone, renin and cortisol by tryptophan. *J. Clin. Endocr. Metab.* **48** (1979) 599–603.
5. Shenker Y., Gross M. D. and Grekin R. J.: Peripheral serotonin 2 receptor blockade does not inhibit 5-hydroxytryptophan-induced aldosterone stimulation. *J. Clin. Endocr. Metab.* **61** (1985) 1201–1203.
6. Maestri E., Camellini L., Rossi G., Dotti C., Marchesi M. and Gnudi A.: Serotonin regulation of aldosterone secretion and production. *Horm. Metab. Res.* **20** (1988) 457–459.
7. Campbell D. J., Mendelsohn F. A. O., Adam W. R. and Funder J. W.: Metoclopramide does not elevate aldosterone in the rat. *Endocrinology* **109** (1981) 1484–1491.
8. Al-Dujaili E. A. S., Williams B. C. and Edwards C. R. W.: The development and application of a direct radioimmunoassay for corticosterone. *Steroids* **37** (1981) 157–176.
9. Haber E., Koerner T., Page L. B., Kilman B. and Purnodo A.: Application of a radioimmunoassay for angiotensin I to the physiologic measurement of plasma renin activity in normal human subjects. *J. Clin. Endocr. Metab.* **29** (1969) 1349–1355.
10. Drury P. L., Williams B. C., Edwards C. R. W., Oddie C. J. and Horne B.: Development and application of a superfusion technique for the study of renin secretion in rat renal cortical cells. *Clin. Sci.* **71** (1986) 581–587.
11. Gow I. F., Corrie J. E. T., Williams B. C. and Edwards C. R. W.: Development and validation of an improved radioimmunoassay for serotonin in platelet-rich plasma. *Clin. Chim. Acta* **162** (1987) 175–188.
12. Zimmermann H. and Ganong W. F.: Pharmacological evidence that stimulation of central serotonergic pathways increases renin secretion. *Neuroendocrinology* **30** (1980) 101–107.
13. Hinson J. P., Vinson G. P., Pudney J. and Whitehouse B. J.: Adrenal mast cells modulate vascular and secretory responses in the intact adrenal gland of the rat. *J. Endocr.* **121** (1989) 253–260.
14. Trost B. N. and Müller J.: Uptake and metabolism of serotonin by rat adrenal tissue *in vitro*. *Acta Endocr. (Copenh.)* **82** (1976) 353–365.
15. Davies E., Rossiter S., Edwards C. R. W. and Williams B. C.: Serotoninergic stimulation of aldosterone secretion *in vivo*: role of the renin-angiotensin system. *J. Endocr.* **130** (1991) 347–355.
16. Henning M. and Rubenson A.: Effects of 5-hydroxytryptophan on arterial blood pressure, body temperature and tissue monoamines in the rat. *Acta Pharmac. Toxic.* **29** (1971) 145–154.
17. Weiner R. I. and Ganong W. F.: Role of brain monoamines and histamine in the regulation of anterior pituitary secretion. *Physiol. Rev.* **58** (1978) 905–976.
18. Krieger H. P. and Krieger D. T.: Chemical stimulation of the brain: effect on adrenal corticoid release. *Am. J. Physiol.* **218** (1979) 1632–1641.
19. Fuller R. W. and Clements J. A.: Role of serotonin in the hypothalamic regulation of pituitary function. *Adv. Exp. Med. Biol.* **133** (1981) 431–444.
20. Shenker Y., Gross M. D. and Grekin R. J.: Central serotonergic stimulation of aldosterone secretion. *J. Clin. Invest.* **76** (1985) 1485–1490.