Psychoneuroendocrinology (2008) 33, 1297—1301

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

SHORT COMMUNICATION

Low plasma tryptophan in carcinoid patients is associated with increased urinary cortisol excretion

Marit A.C. Tanke [a,b,*], Ido P. Kema [c], Janneke Dijck-Brouwer [c], Bennard Doornbos [a,b], Elisabeth G.E. De Vries [d], Jakob Korf [a,b]

[a] *University Center Psychiatry, University Medical Center Groningen, The Netherlands*
[b] *Graduate School of Behavioral and Cognitive Neuroscience, University of Groningen, The Netherlands*
[c] *Department of Pathology & Laboratory Medicine, University Medical Center Groningen, The Netherlands*
[d] *Department of Medical Oncology, University Medical Center Groningen, The Netherlands*

Received 3 March 2008; received in revised form 14 July 2008; accepted 17 July 2008

KEYWORDS
Carcinoid tumor;
Tryptophan;
Cortisol;
Serotonin;
HPA-axis

Summary
Background: Previously we observed in patients suffering from a metastatic carcinoid tumor that irritability, aggression and lack of impulse control are associated with low levels of plasma tryptophan and presumably with low brain serotonin function. In rats we showed that a diet of low tryptophan resulted in higher stress responses and higher corticosterone production. Here we tested in carcinoid patients whether tryptophan depletion due to tumor 5-HT overproduction is associated with high cortisol production.
Methods: Urinary excretion of cortisol, serotonin, 5-hydroxyindole acetic acid (the main metabolite of serotonin a marker of tumor activity), plasma levels of tryptophan and platelet content of serotonin (index of peripheral serotonin synthesis) were determined in metastatic midgut carcinoid patients. Patients ($N = 25$) were divided into two groups based on their plasma tryptophan levels ($\leq$25 μmol/l, $n = 12$ and $\geq$49 μmol/l, $n = 13$).
Results: Carcinoid patients with low plasma tryptophan levels had significantly higher urinary excretion of free cortisol ($p < 0.01$), independent of tumor activity. The inter-individual differences in the low tryptophan group, however, were substantial.
Conclusions: In a subgroup of the patients suffering from metastatic carcinoid disease the cerebral access of plasma tryptophan is impaired, thus rendering cerebral serotonin neurotransmission suboptimal and leading to hypercortisolism. The present study provides further support to the idea that low serotonergic function is a risk for developing stress-associated psychopathology.

Abbreviations: HPA-axis, hypothalamus—pituitary—adrenal-axis; 5-HT, 5-hydroxytryptamine (serotonine); 5HIAA, 5-hydroxyindole acetic acid; CRH, corticotropin releasing hormone; ACTH, adrenocorticotropic hormone.

* Corresponding author at: University Center of Psychiatry, CC64, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel.: +31 50 3612104; fax: +31 50 3611699.
E-mail address: m.a.c.tanke@med.umcg.nl (M.A.C. Tanke).

0306-4530/$ — see front matter
doi:10.1016/j.psyneuen.2008.07.005

1. Introduction

Lasting tryptophan depletion is found in patients suffering from a metastatic serotonin producing carcinoid tumor (Goedert et al., 1980; Kema et al., 1994; Holdcroft, 2000; van der Horst-Schrivers et al., 2004). Carcinoid tumors are rare, malignant but slowly growing tumors that arise from neuro-endocrine cells in the body. Carcinoid tumors secrete a variety of biochemical factors, including serotonin (5-hydroxytryptamine; 5-HT), and 5-hydroxyindole acetic acid (5-HIAA), the main metabolite of 5-HT. By producing 5-HT, the carcinoid uses up to 60% of the body supplies of its precursor tryptophan (Swain et al., 1976). This can result in decreased peripheral tryptophan levels and decreased cerebral availability of tryptophan. Because 5-HT cannot cross the blood–brain barrier, consequently the cerebral synthesis and neuronal release of 5-HT also become limited (Moja et al., 1989).

Chronic depletion of tryptophan as observed in somatic diseases coincides with an increased risk of depression, irritability and aggression (Capuron et al., 2002; Russo et al., 2004, 2005). These symptoms are also associated with alteration in the hypothalamus–pituitary–adrenal (HPA)-axis (Ribeiro et al., 1993; Holsboer, 2000; Parker et al., 2003; Vielhaber et al., 2005; Russo et al., 2007). For example, increased levels of cortisol in plasma, saliva and urine are found in approximately 50% of the patients suffering from a major depressive disorder (Sachar et al., 1973; Owens and Nemeroff, 1993; Holsboer, 2000). When patients recover from the depressive episode, these abnormalities in the HPA-axis activity disappear. Moreover, patients who still have elevated cortisol levels after recovery have an increase risk of relapse (Zobel et al., 1999).

The relationship between the serotonergic system and the HPA-axis, however, is complex. Not only does serotonergic activity influence HPA-axis function (Chaouloff, 2000), but stress and increased HPA-axis activity can – in turn – affect 5-HT function (Fuller, 1996). Furthermore, the effects of chronic and acute alterations in 5-HT are not necessarily the same. Drugs that increase 5-HT function initially stimulate the release of adrenocorticotropic hormone (ACTH) and corticosteroids (Tuomisto and Mannisto, 1985; Bagdy et al., 1989; Di Sciullo et al., 1990; Lucki, 1998; Porter et al., 2004), while long-term use of antidepressive medication suppresses HPA-axis activity (Holsboer et al., 1982; Greden et al., 1983; Gerken et al., 1985; Holsboer and Barden, 1996).

In the present study, we investigate the effect of long-lasting depletion of tryptophan in carcinoid patients on HPA-axis activity. Urinary 5-HIAA concentration is taken as a marker of tumor activity. Platelet content of 5-HT also served as an index of the peripheral synthesis of 5-HT. To our knowledge, there are no clinical studies that link chronic tryptophan depletion with the corticosteroid state in humans.

2. Materials and methods

We retrospectively identified 13/12 patients with normal/low plasma tryptophan levels, respectively in patients with a clinical and biochemically established metastatic carcinoid tumor in the period 2002–2004 at the Department of Medical Oncology, University Medical Center Groningen, The Netherlands. Patients were divided into two subgroups according to their plasma tryptophan levels. The low tryptophan group was defined as having plasma tryptophan levels of 25 μmol/l or less, defined as >2 S.D. below the group mean according to Kema et al. (2001). The normal tryptophan group had plasma tryptophan levels of 49 μmol/l or more. There was no difference in age (61 ± 10 years versus 64 ± 6 years), male/female ratio (4/9 versus 6/6), nor in chronicity of the disease (7 ± 1 years versus 7 ± 2 years) between both groups. The standard treatment of these patients with serotonin overproduction consists of octreotide, which was used in eight patients in the normal tryptophan group and nine patients in the low tryptophan group. Five patients, all in the low tryptophan group were treated with interferon-α. Antidepressants were given to one patient (of the low tryptophan group; mirtazepine).

Blood and 24 h urine samples were obtained once during routine lab investigations during regular morning visits to the outpatient clinic, as described before (Meijer et al., 2000). Plasma Trp and platelet 5-HT concentrations were measured by means of high-performance liquid chromatography (HPLC) with fluorometric detection (Kema et al., 2001). Reference values for plasma Trp are 40–70 μmol/l (Kema et al., 2001). The cut off value for platelet 5-HT is 5.4 nmol/10^9 platelets (Meijer et al., 2000). Urinary serotonin and 5-HIAA concentrations were determined with HPLC/fluorometric detection as described previously (Meijer et al., 2000; Mulder et al., 2005). 5-HIAA levels in 24 h urine were taken as measure for tumor activity (Kema et al., 2000). 5-HIAA is the main metabolite and end-product of serotonin. Cortisol excretion was determined in a urine sample over 24 h. Urine was purified and free cortisol was measured with a validated routinely used ElectroChemiLuminescence ImmunoAssay (ELECSYS, Roche Diagnostics Corporation, Hague Rd, Indianapolis), with streptavidin microparticles. Cortisol was measured in urine to obtain a measure of total cortisol excretion per day. This approach also circumvents variations due to sampling time. Patients were experienced in collecting 24 h urine as this is done routinely twice a year when they visit the Department of Medical Oncology in the UMCG. Reference values for cortisol excretion are 20–270 nmol/24 h.

Statistical analyses were done with SPSS (Version 12.0), with $p \leq 0.05$ as significant. Plasma concentrations of tryptophan and 5-HT, urinary contents of cortisol, 5-HT and 5-HIAA were analyzed using a Mann–Whitney *U*-test. Correlations were noted using Spearman's correlation coefficient. Results are presented as mean ± S.E.M.

3. Results

Subjects with low plasma tryptophan had significantly higher urinary 24 h cortisol excretion (in nmol/24 h) compared to subjects with normal plasma tryptophan levels ($Z - 2.825$; $p = 0.004$, Fig. 1). In the low tryptophan group three patients excreted five times more cortisol than the other subjects. When these patients are excluded the increase in cortisol excretion was still significantly higher in the low tryptophan group (normal Trp ($N = 13$): 51 ± 6 versus low Trp ($N = 9$): 82 ± 1; $Z - 2.170$ $P = 0.03$). The patients that were treated with interferon did not have different cortisol excretion than the other patients in the low tryptophan group. There were no significant differences between the normal and low tryptophan group in platelet 5-HT (17.3 ± 12.9 nmol/10^9 platelets versus 19.2 ± 12.6 nmol/10^9 platelets), urinary 5-HT

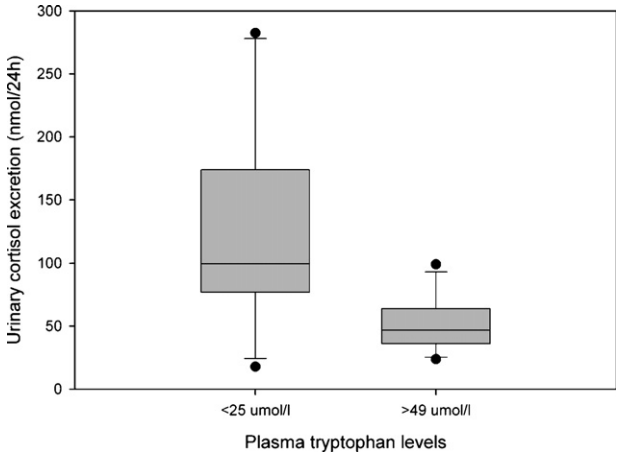

Fig. 1 Twenty-four hours urinary excretion of cortisol in carcinoid patients with low or normal plasma tryptophan levels ($Z - 2.825$, $p = 0.008$).

(1.28 ± 1.75 μmol/24 h versus 17.2 ± 34.9 μmol/24 h) and urinary 5-HIAA levels (0.29 ± 0.57 mmol/24 h versus 0.76 ± 0.73 mmol/24 h).

Correlations between biochemical parameters are shown in Table 1. Plasma tryptophan levels were negatively correlated with urinary cortisol excretion. There was a correlation between cortisol excretion and urinary 5-HT content but cortisol excretion was not correlated with urinary 5-HIAA levels. In contrast with prior observations, we found a positive correlation between plasma tryptophan and urinary 5-HIAA (Kema et al., 2001). However, because this correlation was weak and changed into a negative correlation when excluding the three cases with the highest urinary cortisol levels (see above), we believe that this is not a relevant finding, but merely a statistical coincidence.

4. Discussion

This study confirms our hypothesis that chronic tryptophan depletion in patients suffering from metastatic carcinoid disease is associated with increased cortisol secretion. The data also indicate that the variation in cortisol excretion is far greater in the low tryptophan group as compared to subjects with normal levels of plasma tryptophan.

The strength of this study is that we are able to demonstrate an association between chronic tryptophan depletion and HPA-axis activity in humans. However, carcinoid tumors are rare and the cross-sectional retrospective design of our study in a small patient groups has some drawbacks. First, we do not have longitudinal tryptophan levels. It can be speculated that the patient with the highest urine cortisol levels are the patients with the highest chronic tryptophan depletion or the steepest decline. Second, metastatic carcinoid disease is a stressor that itself may lead to increased production of cortisol. It appeared, however, that tumor activity, as measured by urinary 5-HIAA levels, did not correlate with cortisol levels, suggesting that tumor activity itself did not dictate high cortisol excretion in the low plasma tryptophan group. Third, we cannot exclude that tryptophan depletion is caused by underlying tumor-related causes that itself may alter cortisol excretion, such as reductions in food intake or alterations in immune activation and accordingly indoleamine 2,3-dioxygenase (IDO) activation (Uyttenhove et al., 2003). Decreased dietary intake may decrease plasma levels of tryptophan (Fadda et al., 2000), but not in the extent that is seen in carcinoid patients (Attia et al., 2005). The carcinoid tumor has an extremely high serotonin production and content which drains significantly on the tryptophan pool (Swain et al., 1976; Kema et al., 1992). Fourth, cortisol excretion could be affected by medication. In the low tryptophan group, there was no difference in cortisol excretion between patients with and patients without interferon-α treatment, a cytokine that induces IDO activity and thus lowers tryptophan levels. But because these groups are small, the possibility that the difference in cortisol excretion is caused by a direct effect of either interferon-α or other types of medication cannot be completely ruled out. Fifth, we do not have data on psychopathology of these patients, therefore it cannot be excluded that the cortisol levels are related to underlying psychiatric disorders.

Our study is the first to report increased urinary cortisol excretion being associated with chronic deficiencies in plasma tryptophan levels in humans. Many clinical studies that have focused on the effect of 1–12 h tryptophan depletion reported inconsistent effects on HPA-activity and plasma cortisol (Sobczak et al., 2002; Porter et al., 2002, 2007; Tyrka et al., 2004; Vielhaber et al., 2005). Whereas some (Tyrka et al., 2004; Porter et al., 2007) found increases in CRH in cerebrospinal fluid and plasma cortisol levels, others (Sobczak et al., 2002; Vielhaber et al., 2005) reported decreases in cortisol levels after acute tryptophan depletion. In animal studies also the effect of chronic tryptophan manipulation has been studied. D'Souza et al. (2004) showed that chronic dietary depletion of tryptophan in rats increased resting plasma levels of corticosterone. In addition, dietary supple-

Table 1 Correlations between biochemical parameters (Spearman's rho)

	Plasma tryptophan	5-HT platelets	5-HIAA urine	5-HT urine	Cortisol urine
Plasma tryptophan (μmol/L)	1	−0.307	0.483*	−0.502*	−0.609**
5-HT (nmol/109 platelet)	−0.307	1	0.773**	0.693**	0.108
5-HIAA urine (mmol/24 h)	0.483*	0.773**	1	0.879**	0.337
5-HT urine (μmol/24 h)	−0.502*	0.693**	0.879**	1	0.522**
Cortisol urine (nmol/24 h)	−0.609**	0.108	0.337	0.522**	1

The positive but weak correlation between plasma tryptophan and urinary 5-HIAA changed into a negative correlation when excluding three cases with the highest urinary cortisol levels, therefore we believe that this is not a relevant finding, but merely a statistical coincidence.

* $p < 0.05$.

** $p < 0.01$.

mentation of tryptophan decreased stress evoked cortisol levels in pigs (Koopmans et al., 2005). In a recent animal experiment, decreases in plasma tryptophan only increased plasma corticosterone and adrenal weight in animals which concomitantly received a mild stressor (Tanke et al., 2008). Apparently low plasma tryptophan levels per se do not increase cortisol secretion, but may potentiate the response of the organism to stress, which in turn may activate HPA-activity.

Translating this to the present study, it may well be that suffering from metastatic carcinoid disease is a stressful life event that may lead to increased production of cortisol, particularly in patients with low cerebral availability of tryptophan.

4.1. (Clinical) Implications

We show that chronic depletion of plasma tryptophan levels in carcinoid patients is associated with increased cortisol excretion, and accordingly, increased sensitivity to stress. This might increase the patients' risk to develop stress-related diseases, for example certain psychiatric diseases. Future research should be directed to study the susceptibility to stress and HPA-axis response in humans with chronic low tryptophan levels.

Role of funding source

This study was performed without external funding sources.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

We thank S. Ahmadi and S.A. van Goor for their help collecting the data.

References

Attia, E., Wolk, S., Cooper, T., Glasofer, D., Walsh, B.T., 2005. Plasma tryptophan during weight restoration in patients with anorexia nervosa. Biol. Psychiatry 57, 674—678.

Bagdy, G., Calogero, A.E., Aulakh, C.S., Szemeredi, K., Murphy, D.L., 1989. Long-term cortisol treatment impairs behavioral and neuroendocrine responses to 5-HT1 agonists in the rat. Neuroendocrinology 50, 241—247.

Capuron, L., Ravaud, A., Neveu, P.J., Miller, A.H., Maes, M., Dantzer, R., 2002. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. Mol. Psychiatry 7, 468—473.

Chaouloff, F., 2000. Serotonin, stress and corticoids. J. Psychopharmacol. 14, 139—151.

D'Souza, D.N., Zhang, Y., Garcia, F., Battaglia, G., Van de Kar, L.D., 2004. Fluoxetine-induced changes in body weight and 5-HT1A receptor-mediated hormone secretion in rats on a tryptophan-deficient diet. Am. J. Physiol. Regul. Integr. Comp. Physiol. 286, R390—R397.

Di Sciullo, A., Bluet-Pajot, M.T., Mounier, F., Oliver, C., Schmidt, B., Kordon, C., 1990. Changes in anterior pituitary hormone levels after serotonin 1A receptor stimulation. Endocrinology 127, 567—572.

Fadda, F., Cocco, S., Stancampiano, R., 2000. A physiological method to selectively decrease brain serotonin release. Brain Res. Protoc. 5, 219—222.

Fuller, R.W., 1996. Serotonin receptors involved in regulation of pituitary—adrenocortical function in rats. Behav. Brain Res. 73, 215—219.

Gerken, A., Maier, W., Holsboer, F., 1985. Weekly monitoring of dexamethasone suppression response in depression: its relationship to change of body weight and psychopathology. Psychoneuroendocrinology 10, 261—271.

Goedert, M., Otten, U., Suda, K., Heitz, P.U., Stalder, G.A., Obrecht, J.P., Holzach, P., Allgower, M., 1980. Dopamine, norepinephrine and serotonin production by an intestinal carcinoid tumor. Cancer 45, 104—107.

Greden, J.F., Gardner, R., King, D., Grunhaus, L., Carroll, B.J., Kronfol, Z., 1983. Dexamethasone suppression tests in antidepressant treatment of melancholia. The process of normalization and test-retest reproducibility. Arch. Gen. Psychiatry 40, 493—500.

Holdcroft, A., 2000. Hormones and the gut. Br. J. Anaesth. 85, 58—68.

Holsboer, F., 2000. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 23, 477—501.

Holsboer, F., Barden, N., 1996. Antidepressants and hypothalamic-pituitary—adrenocortical regulation. Endocr. Rev. 17, 187—205.

Holsboer, F., Liebl, R., Hofschuster, E., 1982. Repeated dexamethasone suppression test during depressive illness. Normalisation of test result compared with clinical improvement. J. Affect. Disord. 4, 93—101.

Kema, I.P., de Vries, E.G., Muskiet, F.A., 2000. Clinical chemistry of serotonin and metabolites. J. Chromatogr. B: Biomed. Sci. Appl. 747, 33—48.

Kema, I.P., de Vries, E.G., Schellings, A.M., Postmus, P.E., Muskiet, F.A., 1992. Improved diagnosis of carcinoid tumors by measurement of platelet serotonin. Clin. Chem. 38, 534—540.

Kema, I.P., de Vries, E.G., Slooff, M.J., Biesma, B., Muskiet, F.A., 1994. Serotonin, catecholamines, histamine, and their metabolites in urine, platelets, and tumor tissue of patients with carcinoid tumors. Clin. Chem. 40, 86—95.

Kema, I.P., Meijer, W.G., Meiborg, G., Ooms, B., Willemse, P.H., de Vries, E.G., 2001. Profiling of tryptophan-related plasma indoles in patients with carcinoid tumors by automated, on-line, solid-phase extraction and HPLC with fluorescence detection. Clin. Chem. 47, 1811—1820.

Koopmans, S.J., Ruis, M., Dekker, R., van Diepen, H., Korte, M., Mroz, Z., 2005. Surplus dietary tryptophan reduces plasma cortisol and noradrenaline concentrations and enhances recovery after social stress in pigs. Physiol. Behav. 85, 469—478.

Lucki, I., 1998. The spectrum of behaviors influenced by serotonin. Biol. Psychiatry 44, 151—162.

Meijer, W.G., Kema, I.P., Volmer, M., Willemse, P.H., de Vries, E.G., 2000. Discriminating capacity of indole markers in the diagnosis of carcinoid tumors. Clin. Chem. 46, 1588—1596.

Moja, E.A., Cipolla, P., Castoldi, D., Tofanetti, O., 1989. Dose—response decrease in plasma tryptophan and in brain tryptophan and serotonin after tryptophan-free amino-acid mixtures in rats. Life Sci. 44, 971—976.

Mulder, E.J., Oosterloo-Duinkerken, A., Anderson, G.M., de Vries, E.G., Minderaa, R.B., Kema, I.P., 2005. Automated on-line solid-phase extraction coupled with HPLC for measurement of 5-hydroxyindole-3-acetic acid in urine. Clin. Chem. 51, 1698—1703.

Owens, M.J., Nemeroff, C.B., 1993. The role of CRF in the pathophysiology of affective and anxiety disorders. In: Vale, W., Chichester, (Eds.), Corticotropin Releasing Factor CIBA Symposium. Wiley, pp. 296—319.

Parker, K.J., Schatzberg, A.F., Lyons, D.M., 2003. Neuroendocrine aspects of hypercortisolism in major depression. Horm. Behav. 43, 60—66.

Porter, R.J., Gallagher, P., O'Brien, J.T., 2007. Effects of rapid tryptophan depletion on salivary cortisol in older people recov-

ered from depression, and the healthy elderly. J. Psychopharmacol. 21, 71—75.

Porter, R.J., Gallagher, P., Watson, S., Young, A.H., 2004. Corticosteroid—serotonin interactions in depression: a review of the human evidence. Psychopharmacology (Berl.) 173, 1—17.

Porter, R.J., Marshall, E.F., O'Brien, J.T., 2002. Effects of rapid tryptophan depletion on salivary and plasma cortisol in Alzheimer's disease and the healthy elderly. J. Psychopharmacol. 16, 73—78.

Ribeiro, S.C., Tandon, R., Grunhaus, L., Greden, J.F., 1993. The DST as a predictor of outcome in depression: a meta-analysis. Am. J. Psychiatry 150, 1618—1629.

Russo, S., Boon, J.C., Kema, I.P., Willemse, P.H., Den Boer, J.A., Korf, J., de Vries, E.G., 2004. Patients with carcinoid syndrome exhibit symptoms of aggressive impulse dysregulation. Psychosom. Med. 66, 422—425.

Russo, S., Kema, I.P., Bosker, F., Haavik, J., Korf, J., 2007. Tryptophan as an evolutionarily conserved signal to brain serotonin: molecular evidence and psychiatric implications. World J. Biol. Psychiatry 1—11.

Russo, S., Kema, I.P., Haagsma, E.B., Boon, J.C., Willemse, P.H., Den Boer, J.A., de Vries, E.G., Korf, J., 2005. Irritability rather than depression during interferon treatment is linked to increased tryptophan catabolism. Psychosom. Med. 67, 773—777.

Sachar, E.J., Hellman, L., Roffwarg, H.P., Halpern, F.S., Fukushima, D.K., Gallagher, T.F., 1973. Disrupted 24-h patterns of cortisol secretion in psychotic depression. Arch. Gen. Psychiatry 28, 19—24.

Sobczak, S., Honig, A., Nicolson, N.A., Riedel, W.J., 2002. Effects of acute tryptophan depletion on mood and cortisol release in first-degree relatives of type I and type II bipolar patients and healthy matched controls. Neuropsychopharmacology 27, 834—842.

Swain, C.P., Tavill, A.S., Neale, G., 1976. Studies of tryptophan and albumin metabolism in a patient with carcinoid syndrome, pellagra, and hypoproteinemia. Gastroenterology 71, 484—489.

Tanke, M.A., Alserda, E., Doornbos, B., van der Most, P.J., Goeman, K., Postema, F., Korf, J., 2008. Low tryptophan diet increases stress-sensitivity, but does not affect habituation in rats. Neurochem. Int. 52, 272—281.

Tuomisto, J., Mannisto, P., 1985. Neurotransmitter regulation of anterior pituitary hormones. Pharmacol. Rev. 37, 249—332.

Tyrka, A.R., Carpenter, L.L., McDougle, C.J., Kirwin, P.D., Owens, M.J., Nemeroff, C.B., Strong, D.R., Price, L.H., 2004. Increased cerebrospinal fluid corticotropin-releasing factor concentrations during tryptophan depletion in healthy adults. Biol. Psychiatry 56, 531—534.

Uyttenhove, C., Pilotte, L., Theate, I., Stroobant, V., Colau, D., Parmentier, N., Boon, T., Van den Eynde, B.J., 2003. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat. Med. 9, 1269—1274.

van der Horst-Schrivers, A.N., Wymenga, A.N., Links, T.P., Willemse, P.H., Kema, I.P., de Vries, E.G., 2004. Complications of midgut carcinoid tumors and carcinoid syndrome. Neuroendocrinology 80 (Suppl. 1), 28—32.

Vielhaber, K., Riemann, D., Feige, B., Kuelz, A., Kirschbaum, C., Voderholzer, U., 2005. Impact of experimentally induced serotonin deficiency by tryptophan depletion on saliva cortisol concentrations. Pharmacopsychiatry 38, 87—94.

Zobel, A.W., Yassouridis, A., Frieboes, R.M., Holsboer, F., 1999. Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. Am. J. Psychiatry 156, 949—951.