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SEROTONIN (5-HT) CORRELATES WITH ADIPONECTIN IN OVERWEIGHT PATIENTS

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Abstract
We examined the relationship of two neurohormones with neuroendocrine impact (serotonin /5-HT/ and adiponectin) under standardized clinical conditions in an overweight cohort. Adiponectin was measured in serum and Serotonin was determined in the second morning urine samples. Serotonin correlated positively with adiponectin in our investigation Srho (+0.303; p=0.03). As high adiponectin level corresponds with a low risk of Insulin resistance our findings refer to possible improvement of prediabetic conditions in overweight patients tracking peripheral serotonin circulation. Further clinical evidence is mandatory to verify the effects of 5-HT in patients with metabolic syndrome.

Key words: *serotonin (5-hydroxytryptamine – 5-HT); adiponectin; overweight patients; insulin secretion*

ORIGINAL ARTICLE

INTRODUCTION

Serotonin (5-hydroxytryptamine – 5-HT) is an intermediate product of tryptophan metabolism which is produced primarily in the enterochromaffin cells of intestine, serotonergic neurons of the brain, stored in platelets of the blood and is well established as a neurotransmitter in the central nervous system (CNS). Serotonin issues various inhibitory and exicitatory effects according to different 5-HT receptor families (hydroxytryptamine receptors) spread in the body mainly on the basis of G protein-coupled activation and intracellular second messenger cascade transmission (Wesolowska 2002). Whereas Tph2 related 5-HT activity dominates the homeostasis pulmonary and gut motility, liver regeneration and mammary gland development Tph1 receptor related serotonin activity is confined to control emotional life, mood, pain and perception as well as appetite, sleep and memory (Young 2007).

Lately another serotonin signaling (serotonylation) transmission was discovered by experimental studies linking endocrine insulin secretion of pancreatic ß cells with 5-HT neurotransmitter release. According to this observation insulin secretion is under the control of intracellular and extracellular 5-HT distributions (Paulmann et al. 2009).

There is further clinical prove that brain serotonin not only modifies mood, depression and anxiety but also has an impact on energy management and carbohydrate metabolism (Wurtman and Wurtman 1995).

With this evidence we were concerned to prove a possible interaction between 5-HT and carbohydrate insulin mediated metabolism using sensible biomarkers in a specific cohort with overweight patients and under defined study conditions.

MATERIAL AND METHODS

107 patients with metabolic syndrome were selected from our clinic according to the definition of WHO 1995 without any obvious clasic signs of inflammation. Accordingly n= 47 male with a waist circumference ≥94 cm and n=60 female with a body circumference ≥80 cm were checked for serotonin levels in second morning urine (µg/g creatinine). Adiponectin levels (µg/ml) were determined in blood samples as a surrogate for insulin activity. The assay procedure of serotonin followed the basic principle of a competitive ELISA. The optical density was measured with a photometer at 405 nm (Reference-wavelength: 600–650 nm) within 60 min after pipetting of the stop solution. Second morning urine was used for the determination of serotonin levels. Intra assay and inter precision of the urine test system were 114–625 ng/ml and 105–744 ng/ml respectively. As certain foods contain substantial amounts of serotonin e.g. avocados, bananas, coffee, plums, pineapple, tomatoes, walnuts) patients were advised to refrain from such food with high glcaemic index and not to change their dietary habits for the test period. Also as some medications may cause the release of serotonin and may lead to altered levels volunteers were preselected for the restriction of certain medication (e.g. aspirin, corticotropin, MAO inhibitors, phenazetin, catecholamines, reserpin, nicotin) in this group.

Adipocetin was measured in serum samples of the participants also employing a quantitative sandwich enzyme immunoassay (ELISA) technique. Standards and samples were sandwiched by the immobilized antibody and biotinylated polyclonal antibody specific for adiponectin, which was recognized by a streptavidin-peroxidase conjugate. The minimum detectable dose of adiponectin in this test system was ~0.7 µg/ml. The intra-assay and inter-assay coefficients of variation were 4.3 % and 7.2 % respectively adiponectin levels revealed a gender specific distribution with a normal distribution of >5.6 µg/ml (male) and >7.1 µg/ml (female).

RESULTS

The mean average of serotonin in urine was 151 µg/g creatinine (±161.7) and adiponectin had an overall mean average of 8.02 µg/ml (±4.70) Table 1. Adiponectin results are presented according to the sexual dimorphism of this parameter (Table 2 and 3).

Table 1. Distribution of measurements of serotonin and adiponectin in volunteers (n=103)

	N	Minimum	Maximum	Mean average	Standard deviation
SEROTONIN	103	21.80	1233.80	151.0180	161.7139
ADIPONECTIN	100	1.40	26.00	8.0277	4.7075
Valid results	96				

Male investigated (n=43) had a mean average of 156.5 µg/g creatinine (±174.8) serotonin level in urine and a mean average of 6.78 µg/ml (±4.70) adiponectin in blood of Table 2.

Table 2. Distribution of measurements serotonin and adiponectin in male (n=43) volunteers

	N	Minimum	Maximum	Mean average	Standard deviation
SEROTONIN	43	51.50	1233.80	156.4712	174.7574
ADIPONECTIN	45	2.00	18.70	6.7882	3.5456
Valid results	41				

Female (n=60) showed a mean average of 147.1 μg/g creatinine (±153.0) serotonin level in urine and a mean average of 9.04 μg/ml (±5.29) adiponectin in blood of Table 3.

Table 3. Distribution of measurements serotonin and adiponectin in female (n=60) volunteers

	N	Minimum	Maximum	Mean average	Standard deviation
SEROTONIN	60	21.80	1228.00	147.1098	153.0792
ADIPONECTIN	55	1.40	26.00	9.0418	5.2969
Valid results	55				

Serotonin and adiponectin correlated significantly in female (sRho=+0.003; p=0.003 Table 4) but not in male (sRho=+0.227; p=0.193; Table 5). The overall correlation between serotonin and adiponectin revealed a significant positive correlation (sRho=+0.302; p=0.003 Table 6) as shown in Graph 1.

Table 4. Correlation of serotonin (urine) and adiponectin levels (blood) in female (n=60)

			Serotonin	*Adiponectin*
Spearman-Rho	Serotonin	Correlation	1.000	0.393**
		Sig. (2-sided)	0.0	0.003
		N	60	55
	Adiponectin	Correlation	0.393**	1.000
		Sig. (2-sided)	0.003	0.0
		N	55	55

** Significant correlation on the basis of p<0,01 (two-sided)

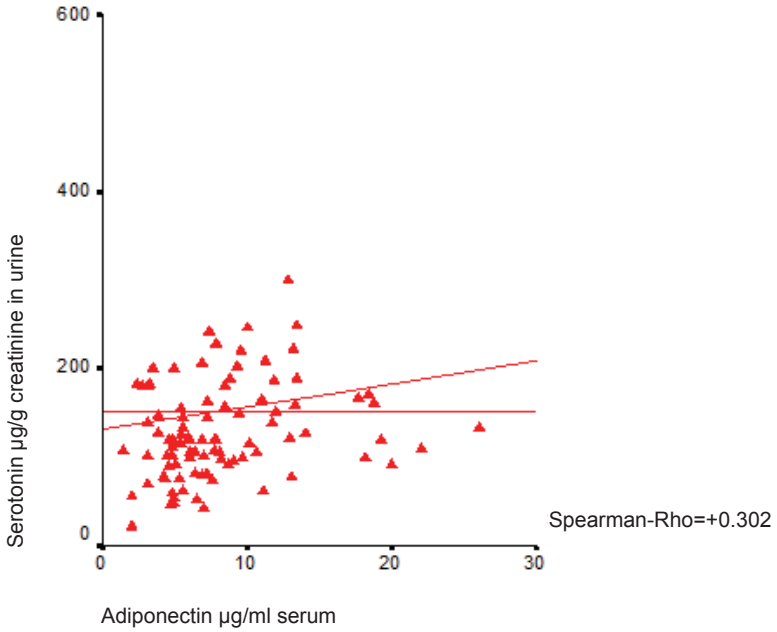
Table 5. Correlation of serotonin (urine) and adiponectin levels (blood) in male (n=43)

			Serotonin	*Adiponectin*
Spearman-Rho	Serotonin	Correlation	1.000	0.193
		Sig. (2-sided)	0.0	0.227
		N	43	41
	Adiponectin	Correlation	0.193	1.000
		Sig. (2-sided)	0.227	0.0
		N	41	45

Table 6. Correlation of serotonin (urine) and adiponectin levels (blood) in all participants (n=103)

			Serotonin	*Adiponectin*
Spearman-Rho	Serotonin	Correlation	1.000	0.302**
		Sig. (2-sided)	0.0	0.003
		N	103	96
	Adiponectin	Correlation	0.302**	1.000
		Sig. (2-sided)	0.003	0.0
		N	96	100

Symbols as in Table 4



Graph 1. Correlation of serotonin levels in second morning urine (µg/g creatinine) and adiponectin in blood (µg/ml) of participants (n=103)

DISCUSSION

Our investigation proved the sexual dimorphism of serum adiponectin values as surrogates of carbohydrate metabolism. Figures from female (n=60) and overall figures (n=103) revealed a significant correlation between 5-HT serotonin and adiponectin (sRho+0.393; p=0.003; sRho +0.302; p=0.003, Table 4, 6).

Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism (Díez and Iglesias 2003). This neurohomone plays a decisive role and counteracts metabolic disturbances that may lead to type 2 diabetes and obesity (Ukkola and Santaniemi 2002). Low levels of adiponectin are therefore considered to be an early risk biomarker of the metabolic syndrome predicting hyperinsulinism and insulin deficiency (Zhu et al. 2010). Adiponectin has been shown to reverse insulin resistance in animal experiment (mice) completely (Yamauchi et al. 2001).

In line with these data our results reveal a protective role of 5-HT in the prevention of metabolic disorders. High levels of adiponectin were found in strong positive correlation with serotonin extinction in patients without pharmaceutical treatment with antidepressants. Evidently low adiponectin levels indicate a higher risk for hyperinsulinemia, insulin resistance and diabetes mellitus. Patients with low serotonin circulation levels produced cor-respondingly low adiponectin serum levels in our investigation with a higher risk for hyperinsulinism and the metabolic syndrome.

This correlation points to a supportive interaction between 5-HT (serotonin) and adiponectin, and allows us to hypothesize a protective impact of 5-HT supplementation on carbohydrate metabolism and insulin activity in overweight patients as preclinical and clinical manifestations of the metabolic syndrome are often characterized by hyperinsulinism (Baumgartner et al. 2012).

Our results are in concordance with other authors who have assumed a diet rich in carbohydrates and low in protein to increase serotonin circulation levels by a higher rate of insulin secretion (Young 2007).

Further clinical studies are mandatory to investigate the exact clinical effect of early oral 5-HT substitution in patients with metabolic syndrome. As serotonin signaling may contribute to anorectic effects this regime may be helpful to reduce sugar cravings and overexessive insulin activity in prediabetic and overweight patients. As hyperinsulinemia and hypoglycemia contributes to a refill with carbohydrate rich and high caloric density food our finding may constitute a novel preventive approach in patients with metabolic syndrome.

CONCLUSION

Previous animal research and studies with human patients revealed a possible neuroendocrine link between serotonin (5-HT) signaling and insulin activity. We investigated such interaction by means of sensitive lab techniques (ELSA). As a surogate of hyperinsulinism and insulin resistance we measured adiponectin levels in a cohort of 103 preselected patients together with 5-HT urine extinction (second morning urine µg/g creatinine). A positive significant correlation between serotonin circulation (second morning urine) and adiponectin levels in blood ($p=0.003$; $sRho=+0.302$) is in favor of a supportive effect between both systems.

These results are in line with our hypothesis that an improvement of peripheral serotonin circulation has a beneficial impact on carbohydrate metabolism and insulin sensitivity. Further intervention studies will be on the way to prove this theory.

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