

Plasma NPY concentrations in women with acute ischemic stroke

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Abstract

OBJECTIVE: It has been reported that plasma NPY levels were increased in obesity, type 2 diabetes mellitus and hypertension. The symptoms of metabolic syndrome frequently appear in patients with acute ischemic stroke. The association between plasma NPY levels and metabolic markers in women with acute ischemic stroke was investigated in the current study.

METHODS: Plasma NPY concentrations were determined using radioimmunoassay in 58 women aged 60–85 (mean age: 76.5±0.8) with acute ischemic stroke and in 24 women aged 63–67 (mean age: 65.6±0.6) of the control group. Stroke was defined according to the NIHSS (National Institute of Health Stroke Scale) and was confirmed using CT or MR scan.

RESULTS: The prevalence of type 2 diabetes, hypertension and insulin resistance was higher in the group of patients with stroke. Plasma NPY levels measured during the 1st day and 10 days after the acute phase of stroke were significantly lower ($p < 0.001$) compared to the control group.

CONCLUSION: In women with acute ischemic stroke plasma NPY concentrations were decreased in spite of higher frequency of the occurrence of the symptoms of metabolic syndrome.

INTRODUCTION

Neuropeptide Y (NPY), a 36 amino acid peptide, was discovered by Tatemoto and co-workers (Tatemoto 1982). It is a member of the pancreatic polypeptide family which also include peptide-tyrosine-tyrosine (PYY) and pancreatic polypeptide (PP) (Tatemoto *et al.* 1982). It plays a major role in the regulation of energy homeostasis, glucose and lipid metabolism as well as insulin secretion (Zhang *et al.* 2011). NPY exhibits biological

actions through specific receptors Y1, Y2, Y3, Y4 and Y5 (Blomqvist & Herzog 1997; Herzog *et al.* 1997; Berglund *et al.* 2003). It has been reported that NPY is widely distributed in the central and peripheral nervous systems, especially in cortical, limbic and hypothalamic regions (Adrian *et al.* 1983) as well as in peripheral regions such as adrenal medulla and sympathetic nervous systems (SNS) where it is co-stored with norepinephrine and epinephrine and cooperates with them (Ekblad *et al.* 1984). An expression of Y1, Y2, Y4,

Y5 receptors was found in the brain and the synthesis of NPY was demonstrated in GABA-ergic neurons (Dumont *et al.* 1998).

NPY was also found to be expressed in the arcuate nucleus (ARC) and in the dorsomedial hypothalamus (DMH). In the arcuate nucleus NPY acts through Y1 and Y5 receptors as a potent orexigenic peptide along with another orexigenic peptide, Agouti-Related Peptide (AgRP). In DMH this peptide plays a role in the thermogenic activity and in maintaining glucose homeostasis (Bi *et al.* 2012).

Interestingly, it has been reported that central injection of NPY leads to increase in food intake and chronic administration to obesity (Zarjevski *et al.* 1993). Moreover, after intracerebroventricular injection NPY may also induce hepatic insulin resistance (van den Hoek *et al.* 2008).

Furthermore, NPY acts as a neuromodulator and influences on release of neurotransmitters such as dopamine and glutamine (Decressac & Barker 2012).

Subsequently, NPY exerts vasoconstrictor action through a NPY-Y1 receptor in the periphery, however in the central nervous system it reveals antihypertensive effects (Michalkiewicz *et al.* 2005).

Finally, some authors suggest that NPY may have a role in the mechanism of cerebrovascular or cardiovascular complications (Brass & Page 1996).

The aim of this study was to investigate the relationship between plasma NPY concentrations and metabolic markers in women with acute ischemic stroke.

MATERIAL AND METHODS

The patients population comprised of 58 women, aged 60–85 years (mean age 76.5 ± 0.8) diagnosed with acute ischemic stroke and 24 women, aged 63–67 years (mean age 65.6 ± 0.6) as the control group.

The stroke patients were hospitalized in the Neurology Department, Second Faculty of Medicine, Medical University of Warsaw, Poland. Control individuals were recruited from the Outpatient Clinic as volunteers. The diagnosis of ischemic stroke was determined with WHO criteria. Stroke severity was assessed according to the National Institute of Health Stroke Scale (NIHSS) criteria. Every stroke patient had a CT brain scan to confirm the diagnosis.

The exclusion criteria were as follows: (1) acute and chronic circulatory failure, (2) acute inflammatory process, (3) acute renal or hepatic dysfunction.

Informed consent was obtained from all the patients or their relatives. The study protocol was approved by the Ethical Committee of the Centre of Postgraduate Medical Education.

The blood samples were collected into tubes containing protease inhibitor (aprotinine) and EDTA during the first day of stroke and 10 days after the acute phase. The blood was centrifuged at 4°C and kept at –70°C until further analysis.

Measurements of glucose were performed using routine laboratory protocol. Insulin plasma concentrations were measured using radioimmunoassay kit (DIA-source ImmunoAssays).

Insulin resistance was estimated using the homeostasis model assessment method (HOMA-IR). HOMA-IR was calculated according to the formula: fasting plasma glucose mmol/l \times plasma insulin concentration μ IU/ml /22.5. Insulin resistance was defined as HOMA >2.5. Plasma NPY concentrations were determined by RIA commercial kit (Peninsula Lab).

The sensitivity of NPY assay was 2 pg/tube and the inter – and intra – assay coefficients of variation were 8.5% and 7.3%, respectively.

Statistical analyses were performed using the Statistica 10 software (StatSoft Inc., Tulsa, OK, USA).

Data are expressed as mean \pm standard error of the mean (SEM). Data were compared between the groups using the Mann-Whitney U-test to identify significant differences. Correlation coefficient was calculated according to the Spearman rank correlation test. The *p*-values less than 0.05 were considered as statistically significant.

RESULTS

The clinical and biochemical characteristic of the study participants are presented in Table 1.

In the group of women with acute ischemic stroke the prevalence of 2 type diabetes, hypertension and insulin resistance (measured with HOMA-IR) was higher compared to the control group.

Plasma NPY concentrations are presented in Table 2. NPY levels in individuals with acute ischemic stroke were significantly lower than those in the control group ($p < 0.001$).

To confirm whether NPY level was associated with BMI, the group of women with stroke was divided into 3 groups: obese with BMI >30 kg/m², overweight with BMI 25–30 kg/m² and lean women with BMI <25 kg/m².

Plasma NPY concentrations in obese subjects (5.38 ± 0.87 pg/ml) did not differ from plasma NPY levels in overweight (4.58 ± 0.54 pg/ml) and lean (6.36 ± 0.79 pg/ml) women. With all participants included in the study significant correlations between NPY and age ($r = 0.54$, $p < 0.001$), and NPY and glucose ($r = 0.25$, $p < 0.05$) were found. No significant correlations were observed between NPY and BMI, as well as NPY and HOMA-IR, and NPY and insulin

DISCUSSION

The present study showed that plasma NPY levels were reduced in patients suffering from acute ischemic stroke. Previous studies have indicated that plasma NPY concentrations were markedly increased in obese patients, especially in those with hypertension or with

type 2 diabetes (Baranowska *et al.* 1997; Milewicz *et al.* 2000; Baranowska *et al.* 2003).

Moreover, elevated levels of NPY were reported in patients with primary and secondary hypertension (Lettgen *et al.* 1994; Pons *et al.* 2004; Baltazi *et al.* 2011; Wocial *et al.* 1995). Consequently, in 2011 Baltazi and co-workers (2011) found that NPY levels were higher in obese and hypertensive subjects than hypertensive but not obese patients.

Furthermore, it has been suggested that NPY may cause a decrease in the insulin sensitivity (Gerick *et al.* 2012) as NPY positively correlated with insulin levels in patients with type 2 diabetes (Ilhan *et al.* 2010). In diabetic patients with the Pro7 allele, elevated NPY levels were correlated with both increased levels of inflammatory molecules and endothelial dysfunction (Jaakkola *et al.* 2010).

In the present study we showed that the incidents of hypertension and diabetes type 2 in women with acute ischemic stroke were markedly higher compared to the control group.

However, BMI in the group with the stroke did not differ to the control group.

Unexpectedly, the NPY concentrations (measured during the first day and 10 days after) were lower in patients with ischemic stroke compared to the controls, despite more frequent prevalence of diabetes, hypertension and insulin resistance.

The exact mechanism of these findings is still unclear although some factors could be taken into consideration. Our previous study indicated that plasma leptin was significantly increased in patients with acute stroke (Grudniak *et al.* 2010). It may be speculated that hyperleptinemia inhibits NPY release in patients with brain infarct.

On the other hand, it has been widely known that disturbed link between NPY and leptin may play a role in the pathogenesis of metabolic syndrome (Kalra 2008). It may also be discussed whether NPY release depends on age. Our previous results demonstrated that plasma NPY concentrations in postmenopausal women were significantly higher compared to the group of young women (Baranowska *et al.* 2000). However, in the oldest-old individuals, centenarians NPY levels were lower than those in 60–70 years old subjects, but being still higher in comparison to young women (Baranowska *et al.* 2007). In addition, a decrease in NPY concentration in centenarians correlated with metabolic markers. Nevertheless, in the current study we observed low NPY levels in women with stroke despite the presence of metabolic syndrome. However, NPY significantly correlated only with age and glucose concentration.

Besides, it has been reported that NPY release depends on sympathetic activity (Zukowska-Grojec 1995; Morris *et al.* 1997) and it is an important stress mediator (Zukowska-Grojec 1995; Kuo *et al.* 2008). Some data indicated that NPY system plays a role in adaptation to stress and in regulation of blood pres-

Tab. 1. Characteristic of the groups under study.

A. Clinical Data

Parameters	Acute ischemic stroke (n=58)	Control group (n=24)
Age (yrs)	76.5±0.8	65.6±0.6
BMI (kg/m ²)	29.6±0.7	28.0±1.4
Obesity (%)	36.5	33.8
Diabetes mellitus type 2 (%)	42.3	19.0
Hypertension (%)	88.4	24.0

B. Biochemical data

Parameters	Acute ischemic stroke	p-value	Control group
Glucose (mmol/l)	7.3±0.3	<0.001	5.8±0.6
Insulin (μIU/ml)	10.9±1.1	ns	8.5±0.9
HOMA - IR	3.4±0.4	ns	2.1±0.3

BMI - body mass index

HOMA - IR homeostasis model of assessment - insulin resistance

Data are presented as mean ± SEM

Tab. 2. Plasma NPY (neuropeptide Y) levels in the study participants.

Peptide	Acute ischemic stroke (1 st day) (n=58)	Acute ischemic stroke (10 th day) (n=42)	Control group (n=24)
NPY (pg/ml)	5.4±0.5	5.6±0.8	24.9±4.3

NPY Acute ischemic stroke (1st day) vs Control group $p < 0.001$

NPY Acute ischemic stroke (10th days) vs Control group $p < 0.001$

NPY Acute ischemic stroke (1st day) vs Acute ischemic stroke (10th days) ns

Data are presented as mean ± SEM

sure (Ruohonen *et al.* 2009), although in patients with posttraumatic stress disorders (PTSD) NPY release was decreased (Rasmusson *et al.* 2010). It is also highly possible that sympathetic activity in acute ischemic stroke is disturbed.

Interestingly, NPY has various pleiotropic effects on central nervous system apart from metabolic activities and vasoconstriction. There are data from literature confirming that through activation of NPY-Y1 receptor NPY modulated vaso-, neuroproliferative as well as immune functions (Kuo *et al.* 2008). In addition, the animal model revealed that activation of NPY-Y2 receptor stimulated proliferation, angiogenesis and macrophage infiltration under conditions of stress (Chronwall & Zukowska 2004; Kuo *et al.* 2008). Moreover, it has been also found that NPY is able to stimulate neurogenesis in the hippocampus and subventricular zone and it may have a part in the mechanism of recovery from stress (Rasmusson *et al.* 2010; Howell *et al.* 1997; Hansel *et al.* 2001).

The results of the animal experiments also supported the thesis of NPY involvement in neuroprotection, in the mechanism of inflammation suppression and production of neurotrophic factors (Decreassac *et al.* 2012).

It is a matter of open debate whether a decrease of NPY release may be connected with an impairment of neuroprotective and anti-inflammatory actions in ischemic stroke. To date, the neuroprotective activity of NPY in neurodegenerative disease is not well understood. (Croce *et al.* 2011, Croce *et al.* 2012). It was observed that activation of NPY-Y1 receptor resulted in NO overproduction and mediated ischemic injury in animals (Chen *et al.* 2002). NPY may increase the risk of cardiovascular and metabolic diseases during chronic stress (Abe *et al.* 2010). Data from recently published study provided an evidence of the association between the NPY gene and susceptibility to ischemic stroke. In populations of Chinese and Korean patients NPY polymorphisms have been demonstrated (Kim *et al.* 2009; Yu *et al.* 2010; Ko *et al.* 2012). These results may suggest that NPY may be an important factor in the stroke mechanism.

In the future, joined genetics, endocrinology and biochemistry studies may explain the involvement of NPY in the mechanism of ischemic stroke.

CONCLUSION

In women with acute ischemic stroke plasma NPY concentrations were decreased in spite of more frequent occurrence of the symptoms of metabolic syndrome.

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