Acta Biomedica Scientia
e - ISSN - 2348 - 2168
Print ISSN - 2348 - 215X
www.mcmed.us/journal/abs
Research Article

EXPLORING THE DYNAMICS OF NEUROPEPTIDE Y (NPY), SYMPATHETIC ACTIVITY, AND FEEDING BEHAVIOR IN EXPERIMENTAL TYPE 1 DIABETES: A FOCUS ON THE PARAVENTRICULAR NUCLEUS (PVN) OF THE HYPOTHALAMUS

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ABSTRACT

NPY modulates sympathetic activity and feeding behavior by interacting with norepinephrine neurons. The level of NPY in the hypothalamus is correlated with sympathetic activity in diabetes, but little effort has been made to identify the relationship between NPY and sympathetic activity in experimental type 1 diabetes. The male Sprague Dawley rats were instilled with streptozotocin (65 mg/kg body weight) intravenously to induce diabetes. The animals were examined again after two weeks, four weeks, and eight weeks. Animals in the control group were only given citrate vehicle. For clarifying the modulatory effect of NPY at early stages of diabetes, the paraventricular nucleus (PVN) of the hypothalamus was microdialyzed. NPY levels jumped almost immediately after streptozotocin injection, while norepinephrine levels were not increased for 8 weeks after injection. Significant weight loss was observed in the animals. PVN feeding behavior and NPY levels are strongly correlated, based on these results. Following diabetes, NPY receptors may be down-regulated since NPY inhibits sympathetic activity. Animals did not gain weight despite higher norepinephrine levels indicating high sympathetic activity. Additionally, NPY is controversial because of its actions as a pleiotropic in relation to the behavioral aspects of feeding in these animals.

Keywords: - A streptozotocin treatment increases sympathetic activity and feeding habits due to a decrease in NPY receptor expression.

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Received:20.07.2022	**Revised**:02.08.2022	**Accepted**:10.08.2022

INTRODUCTION

In addition to controlling many bodily functions, the hypothalamus also controls diabetes. The paraventricular nucleus (PVN) produces neuropeptide Y (NPY) when catecholamines colocalize with it. Another peptide, leptin, acts through NPY to regulate body weight, energy balance, and sympathetic tone3–4. Adipocytes produce leptin, a circulating hormone that increases in the plasma of obese and type 2 diabetic individuals. NPY-leptin axis regulation regulates food intake, energy expenditure, and obesity in type 2 diabetes through decreased sympathetic activity. 5–7 In type 2 diabetes, leptin suppresses NPY activity through decreasing sympathetic activity.

In type 1 diabetes, which is caused by a defect in insulin availability, the NPY does not play a direct role in sympathetic activity. Experimental type 1 diabetes

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animals, however, exhibited no weight gain despite. increased NPY levels in the hypothalamus. In order to determine whether NPY-leptin axis or NPY-sympathetic activity are responsible for regulating food intake, we must consider how they interact. When insulin deficiency causes insulin-deficient diabetic rats to overeat, this is attributed to insulin (or leptin) inhibiting NPY synthesis and increasing sympathetic activity. NPY levels are higher in PVN animals than in diabetic animals.2,9 Still, PVN animals do not gain weight even though their sympathetic activity is elevated. Our aim was to investigate how type 1 diabetes progresses based on NPY and norepinephrine levels in PVN following streptozotocin injection. The purpose of this study was to correlate body weight and feeding behavior with NPY and sympathetic activity. Streptozotocin injections resulted in an increase in sympathetic activity (not a decrease), so the NPY-leptin axis was not evaluated after 8 weeks

METHODS

Male Sprague-Dawley rats (175–200 g) were rendered diabetic by intracathed streptozotocin administered in a citrate-buffered vehicle (pH 4.5). A control group of normal rats was inhibited with citrate buffer alone. A constant supply of food and water was provided to all rats throughout the experiment. The diabetic animals were divided into three groups. After streptozotocin injection, the diabetic and control animals were matched accordingly. Prior to sacrifice, animals in the second group received subcutaneous injections of protamine zinc insulin.

An analysis of plasma samples was conducted to determine the levels of glucose and insulin. Research protocols were approved by the Animal Care Committee at Arabian Gulf University and small animals were used and handled according to guidelines. PVN extracellular fluid was collected via microdialysis experiments, as previously described. A stereotaxic instrument guided a microdialysis probe during anesthesia with 40 mg ketamine and 4 mg xylazine. As a result of a one-hour microdialysate separation, NPY and norepinephrine levels were determined using a high-pressure liquid chromatography system. Microdialysis experiments were carried out as previously described, 11,12 and NPY and norepinephrine levels were determined. Analyzing the results was done by using factorial analysis of variance. A statistical analysis of all groups was carried out using Scheffe's post hoc test. P values less than 0.05 were considered significant differences between two groups.

RESULTS

The different experimental groups have different characteristics. It was not surprising that after eight weeks, this group's mean body weight was significantly lower than the control group following strepto-zotocin injection. The blood sugar levels of these patients were also significantly depressed resulting in severe hyperglycemia. Diabetic animals, however, consumed more food. Several previous reports have reported similar characteristics. [1, 2] The 4-week diabetic animals were given 3 U insulin daily for 2 weeks in order to reverse the changes observed. A microdialysis sampling of the PVN of the hypothalamus at different stages of diabetes results in different levels of extracellular norepinephrine and NPY. Diabetes resulted in a significant increase in NPY levels; however, norepinephrine levels didn't increase until 8 weeks later. Following 8 weeks of diabetes, the norepinephrine concentration in the blood was 12.8 x 1.5 compared to 1.1 x 0.4 in control animals. P value was below 0.05 to show that such an increase was statistically significant. Norepinephrine levels in diabetic subjects after four weeks of insulin treatment had decreased to 4.6. This suggests that increased sympathetic activity is to blame. Diabetes also produces activity (including cardiomyopathy after eight weeks of study). In diabetics, NPY levels rapidly increase (control 12/1; two weeks after diabetes, 55/8). There was also a statistically significant difference with a P value less than 0.05. In addition, the NPY level continued to rise after diabetes for eight weeks. In this case, insulin treatment partially reversed 20x3 levels, so there appears to be no arti-factual component.

DISCUSSION

In addition to regulating body weight, energy balance, and sympathetic tone, NPY also regulates body temperature. It was found that NPY suppresses sympathetic activity in interscapular brown adipose tissue, having a predominant suppression effect. As a result, NPY modulates sympathetic nervous system activity to affect energy expenditure. The main feeding effect of NPY is caused by NPY/agouti-related peptides that project into PVN of the hypothalamus. Due to insulin (and leptin) inhibiting NPY synthetase, obese people and those with noninsulin diabetes (type 2) have been suggested to be more resistant to insulin (and leptin) inhibition, possibly due to stimulation of arcuate nucleus-PVN peptide projection. Compared to previous studies, our study's animals (type 1 diabetic) displayed hyperphagia, sympathetic inhibition, reduced energy expenditure, and increased weight gain, exhibiting significant differences in behavioral characteristics. Although streptozotocin injections increased NPY levels, sympathetic activity did not decrease afterward. In PVN, NE levels were significantly higher at later stages of diabetes because of increased sympathetic activity.

NE content, turnover, synthesis, and release in 8-week diabetic rats also showed higher sympathetic tone. Our model does support greater energy expenditure

and weight loss due to higher sympathetic activity, but it was unable to explain why the sympathetic activity would increase with NPY levels higher. NPY receptors may have been deregulated after diabetes developed, which is why hypertension and congestive heart failure cannot elicit inhibition as often happens with NPY receptors.

Insulin regulates the sympathetic nervous system, according to now compelling evidence. A significant increase in Euglycemic clamping induced by insulin causes a regional spillover and a rise in plasma catecholamine concentrations. It is likely that such sympathetic activity will occur when insulin availability or production aren't affected in type 2 diabetes. According to these data, type 1 diabetes (insulin-dependent) differs from type 2 diabetes in its central mechanisms governing appetite, body weight, and sympathetic regulation. NPY levels After a brief period of time, the hypothalamus directly controls body weight and feeding behavior. Studies will certainly be interesting to look at how streptozotocin affects NPY receptors after diabetes induction. NPY receptors are downregulated in congestive heart failure, which increases norepinephrine levels.

CONCLUSION

Based on our findings, NPY plays a unique role in diabetes of different types. With type 1 (insulin-dependent) diabetes, NPY levels increase and sympathetic tone is stronger, energy expenditure is higher, and weight loss occurs. In diabetes type 2 (insulin independent) with a high level of NPY, decreased sympathetic tone can mimic obesity. Leptin's role in hypothalamic energy balance is especially relevant in situations such as type 2 diabetes..

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Cite this article:
Dr Santosh Mohanlal Modani, Dr Apuroopa Kunireddy. (2022). Exploring the Dynamics of Neuropeptide Y (NPY), Sympathetic Activity, and Feeding Behavior in Experimental Type 1 Diabetes: A Focus on the Paraventricular Nucleus (PVN) of the Hypothalamus. *Acta Biomedica Scientia*, 9(2), 58-61.