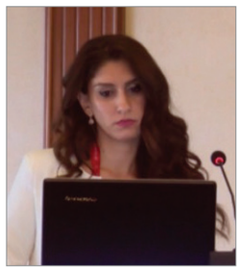
Neuropeptides Y: Biomarker or predictor of hypertension in obesity?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SUMMARY

Obesity is a modern disease that tends to become a pandemic. Its pathophysiology is multifactorial and often the involved mechanisms are overlapped, while they are not fully specified. The phenomenon of maintaining energy homeostasis consists of the central and the peripheral part and their interaction is mainly processed through neuropeptides. Depending on their function, neuropeptides are classified to either appetizing or anorectics, and moreover, to either central or lateral. The major central orexigenic peptide is the neuropeptide Y (NPY), which plays a primary role in energy homeostasis, mainly by regulating thermogenesis in adipose tissue. Furthermore, beyond the regulation of thermogenesis, NPY participates in the regulation of many other physiological functions of the human body, while the level of NPY could result the contribution of overactive Sympathetic Nervous System (SNS) in the pathogenesis of arterial hypertension (HTN) in obese people. The aim of this review is to summarize and fully understand the role of NPY in obesity and arterial hypertension and in particular in hypertension in obese people.
Key words: NPY, obesity, hypertension

Νευροπεπτίδιο Υ: Βιοδείκτης ή δείκτης πρόβλεψης στην Αρτηριακή Υπέρταση στους παχύσαρκους;

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ΠΕΡΙΛΗΨΗ

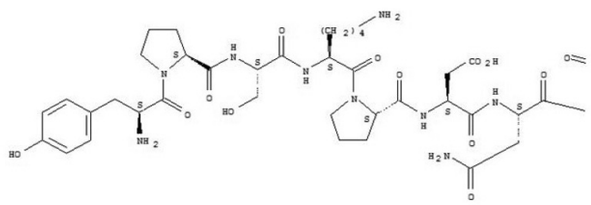
Η παχυσαρκία αποτελεί μία σύγχρονη νόσο που τείνει να λάβει διαστάσεις πανδημίας. Οι παθοφυσιολογικοί μηχανισμοί που εμπλέκονται είναι περίπλοκοι και αλληλεπικαλυπτόμενοι, ενώ ταυτόχρονα δεν είναι πλήρως διευκρινισμένοι. Ο μηχανισμός διατήρησης της ενεργειακής ομοιοστασίας αποτελείται από την κεντρική και την περιφερική μοίρα και η επικοινωνία τους γίνεται, κυρίως μέσω των νευροπεπτιδίων. Τα νευροπεπτίδια διακρίνονται ανάλογα με τη δράση τους σε ορεξιογόνα και ανορεξιογόνα, κεντρικά και περιφερικά. Το σημαντικότερο κεντρικό ορεξιογόνο πεπτίδιο είναι το νευροπεπτίδιο Y (NPY), το οποίο διαδραματίζει πρωτεύοντα ρόλο στον μηχανισμό της ενεργειακής ομοιοστασίας, κυρίως μέσω ρύθμισης της θερμογένεσης στον λιπώδη ιστό. Παράλληλα το NPY, πέραν της ρύθμισης της θερμογένεσης, συμμετέχει στη ρύθμιση πολλών φυσιολογικών λειτουργιών του ανθρώπινου οργανισμού, ενώ τα επίπεδα του NPY πιθανόν να αντανακλούν την συμμετοχή της αυξημένης δραστηριότητας του Συμπαθητικού Νευρικού Συστήματος (ΣΝΣ) στην παθογένεση της Αρτηριακής Υπέρτασης (ΑΥ) στην παχυσαρκία. Σκοπός αυτής της ανασκόπησης είναι η σύνοψη και κατανόηση του ρόλου του NPY στην παχυσαρκία και την ΑΥ και πιο συγκεκριμένα, στην ΑΥ στους παχύσαρκους.

Λέξεις-κλειδιά: NPY, παχυσαρκία, αρτηριακή υπέρταση

NPY

NPY constitutes a central orexigenic, which, along with the peptide YY (PYY) and the pancreatic polypeptides belong to the "family" of the pancreatic peptides. The pancreatic peptides are distributed both in the central and the peripheral nervous system.[1] (Fig.1).

Fig-1: NPY chemical structure



There have been identified five subtypes of NPY receptors which are connected with G proteins. These subtypes are Y1, Y2, Y4, Y5 and y6.[2]

NPY expression and food intake regulation

Centrally, NPY is translated in many places like hypothalamus, amygdaloid nucleus, hippocampus, nucleus tractus solitaries (NST) and spinal cortex.[3] High consecration of NPY is mainly found in adrenal glands.[4] In periphery, NPY is found in various positions and that indicate the diverse role of NPY. This role is not limited to the regulation of energy homeostasis but also extends to other functions.[5]

Control of the homeostasis of energy is firstly determined by the secretion of NPY, leptin, insulin, ghrelin and secondarily by the secretion of other peripheral neuropeptides.[6] Leptin and insulin penetrate the blood-brain barrier and suspend the neuronal activity of NPY/AgRP(agouti-related peptide) neurons. At the same time, insulin and ghrelin boost the neuronal activity of pre-opium-melanocortine/ cocaine and amphetamine regulated transcript (POMC/CART) whose role is to suspend food intake.[7,8] On the other hand, ghrelin which is secreted by the stomach and the duodenum, activates the NPY/AgRP neurons in the Arctuate nucleus of hypothalamus (ARC), boosting this way the food intake.[9]

NPY's composition and secretion increases during periods of energy shortage. This shortage can be caused by a reduction in the amount of food ingested or by a high demand on energy. ARC's neurons produce NPY so that the energy balance can be restored during these periods of energy shortage.[10] On the other hand, in the case of obesity caused by a volitional increase of one's amount of food ingested, (not compensatory) there hasn't been noticed increased activity if the ARC neurons which produce NPY. Contrary, there is evidence of a decrease of this activity, most probably resulting from our organism's effort to reduce unnecessary energy storage.[11]

One main route through which the NPY of ARC and DMH (dorsomedial hypothalamus) regulates the energy balance via the Sympathetic Nervous System (SNS), is the regulation of thermogenesis and the effect both in the white adipose tissue (WAT) and the brown adipose tissue (BAT).[5]

NPY co-exists within the terminal neuron with Norepinephrine (NE) and adenosine triphosphate in the SNS's postganglionic fibers throughout the body, and is released in amounts proportional to the intensity of the excitation of SNS.[12] The increase of NPY in the hypothalamus suppresses the release of catecholamines, primarily of NE through the SNS, and therefore reduces the lipolysis related to the cyclic AMP (cAMP)- A protein kinase (PKA) via b-adrenergic receptors. On the other hand, NPY which exists in the peripheral, stimulates lipogenesis, where the ERK (Extracellular Regulated Kinases) mediate. The reduction of SNS tone is counterbalanced by catecholamines, particularly by adrenalin, which stimulates adipogenesis, probably by regulating NPY.[13]

Obesity is characterised by the large number and the hypertrophy of WAT cells, especially in visceral fat, but also by the alterations of SNS activity, which includes increase of lipid storage and decrease of acidosis.[14]

Peripherally, NPY binds to Y1, Y2 and Y5 receptors and acts on b-adrenergic receptors (b1, b2, b3), amplifying their connection with G-proteins, a fact that leads to inhibition of adenylyl cyclase (AC) and c AMP production. The reduced levels of cAMP inhibit PKA phosphorylation, which activates the hormone-sensitive lipase (HSL). At the same time, PKA' s reduced activity inhibits the phosphorylation of a group of proteins (peri), which control the amount of lipolysis.[15]

As for the effect of NPY on BAT, this is performed via reduction of SNS tone and thermogenesis control. Increasing levels of NPY in hypothalamus reduce SNS tone -especially reducing NE's activity- and, consequently, the signaling of cAMP-PKA is via b- adrenergic receptors inhibited. Reduced lipolysis is responsible for the reduction of fatty acid storage in BAT and, also, the reduction of expression and secretion of UCP1 protein, a fact that causes decrease in thermogenesis.[16]

Given the fact that NPY controls the production of adipose tissue, in combination with the fact that NPY levels are increased in ARC, in exposure to chronic stress[17] and under circumstances of long-term, high fat content diets, we can come to a conclusion that increasing NPY levels in ARC contribute to obesity development, since they promote food intake and energy costs reduction.[10]

In the peripheral nervous system, NPY is expressed in sympathetic neurons, myenteric Auerbach's plexus and submucosal nerve plexus of intestine nervous system. NPY is also synthesized and released by pancreatic islet cells via Y1 receptor and inhibits the glucose-induced insulin secretion. High NPY levels are observed after SNS stimulation and in patients suffering from pancreatic endocrine tumors, carcinoid tumors, neurogenic tumors, including neuroblastoma and pheochromocytoma. In gastrointestinal system, NPY causes reduction of fluid and electrolyte secretion and, also, reduction of stomach and small intestine movement. Intravascular administration of NPY in visceral circulation is related to vasoconstriction, something that can't be reversed with a- or b- blockers administration.[18]

Hypertension and obesity

The mechanisms through which obesity causes blood hypertension have been studied both on human, as well as on experimental models (animals). It seems that there is a variety of mechanisms in blood pressure (BP) variability, such as derivatives of fatty tissue, neuro-hormone mechanisms, metabolic functions and multiple other factors.[19]

More specifically, hypothalamus, hemodynamic changes -such as Sodium retention- and also kidney structural changes, renin-angiotensin- aldosterone system (RAAS), increased SNS stimulation, low sensitivity of baroreceptors' reflex, high levels of free fatty acids in plasma and increase of activity of high levels of angiotensin in plasma contribute to the pathophysiological mechanism. Furthermore, hyperinsulinemia and increased insulin resistance, hyperleptinemia and increased leptin resistance, neuropeptides such as NPY, ghrelin and adiponectin, corticosteroids, vascular endothelium disfunction, high levels of endothelin-1 and reduced carbon monoxide (CO) synthesis play a role in Hyprtension (HTN) of obese people. Consequently, high BP in obesity is the result of the combination or even duplication of the factors described above.[19]

Is there a link between NPY and obesity Hypertension?

According to recent studies, it seems that NPY plays a role in central cardiovascular system regulation, since researches performed both on human and on experimental mice prove that central and peripheral NPY is involved in the development and maintenance of HTN.[20]

In particular, researches performed on human show that NPY levels in plasma are higher in people with HTN, even in non-dippers (less than 10% drop in blood pressure during sleep).[21] The same applies to mice with essential HTN. Researches performed on experimental mice with HTN, show that NPY's neural network is thicker and NPY levels are higher compared to mice with normal BP. The increase of NPY neural network's neurosis increases with age and precedes development of HTN.[22] Specifically, it's been proved that the expression of Y2 receptors in mice increases during the early phase of HTN development. [23]

NPY injection in posterior hypothalamic nucleus and/or into cerebral ventricles, in mice with HTN, seems to be enhancing high BP.[22] Meanwhile, administration of NPY's Y1 antagonist (BRC-672) caused drop in BP.[24]

It has been noticed in rats with essential HTN, that the activity of NPY receptors and α2 adrenergic receptors is decreased presynaptically. This fact leads to reduced retrograde regulation of NE and NPY release, during periarterial neuron stimulation.[25] These data suggest that increase of SNS tone combined with changes in presynaptic NE and NPY inhibition in sympathetic neurons could be a significant factor contributing in development and maintenance of HTN.[22]

Data from last decade attach a new role to NPY and its effect on cardiovascular system. It seems that NPY stimulates the proliferation of cells of vascular smooth muscle fibers. This action was initially found to be performed via Y1 receptors, even in lower NPY levels than the ones causing vasoconstriction.[26,27]

Specifically, sympathetic nerves innervating blood vessels, synthesize, store and release NE, NPY and adenosine triphosphate (ATP). ATP mediates rapid phase, NE mediates in the intermediate phase and NPY mediates in the long-term phase of SNS induced vasoconstriction. Stimulation of the periarterial nerve promotes Na+ entry into presynaptic neuron and leads to neuron depolarization and Ca++ entry into presynaptic neuron. High levels of Ca++ facilitate vesicle fusion, that contain NE, NPY and ATP, which are released in the synaptic cleft. Thus, NE, NPY and ATP subsequently stimulate respectively a1, Y1 and P2X postsynaptic receptors, which are placed in cells of vascular smooth muscle. Stimulation of these receptors resulted in vasoconstriction. NE, NPY and ATP (and several other transmitters) also have the ability to stimulate the corresponding presynaptic receptors (A2, Y2 and P2Y) achieving negative retrograde regulation of their release.[22]

Furthermore, vasoconstriction caused by NPY itself or NPY together with other vasopressors (such as NE and vasopressin) is stronger in the arteries of mice with HTN compared to mice with normal BP.[28] It has been noticed that the response of vessels and BP to NPY increases at the same time with HTN development, in mice with HTN.[29] Meanwhile, NPY controls the release of NE from SNS neurons and catecholamine neurons, centrally, via negative retrograde regulation.[30]

A study has proven that during paroxysms in pheochromocytoma, NPY levels increase simultaneously with catecholamine levels increase. This fact shows there is a link between NPY and secondary HTN.[31] The amount of NPY receptors in hypothalamus of mice with HTN is reduced, something that can be a reflex regulation of high NPY levels. This reduced receptors' number might be responsible for increased catecholamine secretion, which leads to BP increase.[32] The inhibitory NPY action on NE secretion is performed via Y1R.[33]

High NPY levels are directly involved in increase of BP in obese people with HTN, by causing vasoconstriction via Y1 receptors.[34] High NPY levels present in obesity and other situations characterized by increased SNS activity, such as anxiety, body exercise, cardiac failure, myocardial ischemia, toxic and hemorrhagic shock. Unlike, catecholamines, NPY is not responsible for basic vascular tone, but its vasoconstrictive properties increase in stress situations, reinforcing NE's activity, causing vasoconstriction and BP reinstatement. Therefore, increased SNS activity reinforces NPY's vasoconstrictive activity, and subsequently, NPY reinforces vessels' sensitivity in catecholamines.[20,35,36]

NPY is related with hypoglycemia, due to reduced insulin, that causes SNS tone increase and BP increase.[37] Subcutaneous NPY administration in rats causes sequential increase of NPY in plasma, adrenals and upper cervical ganglia. This fact shows that release, biosynthesis and storage of NPY are increased after hypoglycemic stress. It has been noticed that NPY seems to play a significant role in HTN associated to insulin decrease.[22]

Intravenous NPY administration causes renal vasoconstriction, which is associated to HTN[38,39] and certainly NPY's effect is stronger on the efferent than on the afferent arteriole.[40,41] NPY seems to be strongly involved in the degree of HTN in patients with Chronic Kidney Disease, under hemodialysis.[42]

High NPY levels in plasma are related with fluid excess degree and mean arterial pressure. During stress situations, such as fluid excess, NPY release creates a vicious circle: NPY aggravates HTN and increases cardiac load, therefore risk of cardiac failure. Inductively, cell stress increases and SNS is stimulated.[43]

NPY is associated with ischemic strokes and their outcome.[44,45] It is also associated with atherosclerosis, whereas total cholesterol and triglyceride levels increase and HDL levels decrease.46

Genetic studies also associate NPY with high BP.[47] Carriers of T1128C NPY gene polymorphism are proved to have an increased risk of HTN, related with myocardial infarction and ischemic strokes.[48-50]

Based on several studies, both atrial and ventricular myocardium cells contain high amounts of NPY. In experimental animals, NPY has also been detected in the endings

of nerves which innervate myocardium and coronary arteries.[26,51] Thus, NPY participates in myocardial function both indirectly- increasing afterload through vasoconstriction- and directly-mediating in coronary vessels constriction and myocardial cells contraction. Other studies mention that NPY stimulates myocardial cells' hypertrophy in experimental animals, probably via its participation in hypertrophy observed in HTN.[51-53]

Furthermore, studies show that NPY plasma levels are increased after acute coronary syndromes and cardiac failure. These levels are positively associated with the degree of cardiac failure and mortality. On the contrary, NPY levels in insufficient cardiac muscle seem to be strongly reduced compared to NPY levels in normal cardiac muscle. The same thing happens to NE levels, a fact which proves that NPY levels follow SNS activity.[26]

In conclusion, it seems that NPY contributes to the development and maintenance of HTN, both directly and indirectly, mainly via SNS stimulation. Also, NPY promotes HTN target organs damage (such as brain, heart, kidneys and vessels) both via SNS, RAAS and indirectly.

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