

Neuropeptide Y Receptors: Future Therapeutic Target in Congestive Heart Failure

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Peptides are known to be widely distributed in the body, particularly in the gut and the nervous system. In 1982, the presence of a novel brain peptide, neuropeptide Y (NPY) was reported. Subsequently, it was established that NPY is colocalized and co-released with norepinephrine and is distributed in both the central and the peripheral nervous systems. Other reports have indicated the possible role of NPY as a neuromodulator for the catecholaminergic neurons. Since altered sympathetic activity plays a crucial role in the pathophysiology of congestive heart failure, we examined the role of NPY in the modulation of sympathetic activity in various cardiovascular diseases including congestive heart failure. This review article will provide an insight into the status of the NPY receptor and the possible therapeutic targets in congestive heart failure.

Key words — neuropeptide Y, congestive heart failure, pre-synaptic inhibition, sympathetic activity, vasoconstriction

Currently, there is a general agreement about the alterations of sympathetic activity in a variety of cardiovascular diseases and their complications.¹⁾ This understanding is strengthened by the fact that various drugs, which alter the sympathetic activity, are also therapeutically effective in these cardiovascular disorders.

The involvement of catecholamines in congestive heart failure has been known for a long period of time. It is now obvious that the myocardium of patients with heart failure is depleted of norepinephrine in spite of the fact that circulating levels of norepinephrine are considerably elevated.¹⁾ There are reports which suggest that plasma norepinephrine is a good indicator of prognosis in patients with congestive heart failure, probably more important than any other variable with the exception of left ventricular ejection fraction.²⁾ The question, therefore, arises as to what initiates the heightened sympathetic tone in congestive heart failure? This article will provide a brief overview of the sympathetic nervous system in heart failure, with a specific focus on the interaction with neuropeptide Y (NPY), which is coreleased and colocalized with norepinephrine.

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Sympathetic Activity and Congestive Heart Failure

Congestive heart failure remains one of the biggest clinical problems for mankind. Millions of people every year suffer from myocardial dysfunction and even with the latest techniques in diagnosis and treatment, many of them die. The failure of the heart produces a serious imbalance between the demand and supply in an organ which unfortunately can not be maintained for long and inevitably progress towards a fatal conclusion begins unless a successful restoration program is instituted.

A rise in plasma norepinephrine has always been observed in heart failure.¹⁾ Although the exact cause of this heightened sympathetic drive is unknown, it has been postulated that the increase in the sympathetic outflow is likely to be mediated by the arterial stretch receptors.³⁾ It is believed that these receptors send impulse to the brains that inhibit two vasoconstrictor mechanisms: the sympathetic outflow and the release of vasopressin from posterior pituitary. When these afferent inhibitory impulses are decreased due to a fall in systemic arterial pressure, the central tonic inhibition is reduced, thereby increasing the sympathetic tone and the release of norepinephrine.⁴⁾

Many investigators have proposed that the activation of this powerful system is not at all benefi-

cial to patients with heart failure.⁵) In congestive heart failure the ability of atrial and arterial baroreceptor to suppress sympathetic activity is markedly impaired. The cause of this desensitization of baroreceptors is not known, but its effect is to shift the balance of circulatory homeostatic mechanisms to a stage in which the circulating levels of catecholamines are increased and therefore, are not beneficial in the long run. This neuroendocrine system will allow increased ventricular afterload and poses a greater workload on the myocardium, causes further deterioration of the cardiac pump and worsens the heart failure. This is complicated by the fact that lack of responsiveness of the myocytes to postganglionic sympathetic stimulation reduce the increase in output necessary to maintain blood pressure.⁶)

It may be pointed out that the role of the renin-angiotensin system, aldosterone and atrial natriuretic peptide should be taken into consideration in understanding the pathophysiology of congestive heart failure, however, this aspect will not be dealt with in this review.

Neuropeptide Y and Its Receptors

The colocalization of NPY with catecholamines, its role in presynaptic inhibition as well as its distribution throughout the central and peripheral nervous system prompted scientists all over the world to identify the precise nature of NPY neuromodulation^{7,8}) and explore the possibility of therapeutic use of NPY agonists and antagonists in different cardiovascular diseases associated with altered sympathetic activity.

NPY was initially isolated as a by-product while Kimmel *et al.*⁹) isolated insulin from the chicken pancreas and named it pancreatic polypeptide (PP). Tatemoto and Mutt¹⁰) subsequently reported that porcine brain and gut contained large amounts of a peptide resembling PP. This PP-like peptide isolated from gut was named peptide YY (PYY) because of its N- and C-terminal tyrosine (Y being the abbreviation for tyrosine in the single letter amino acid code). Subsequently, it was named neuropeptide Y because of its occurrence in the brain.

NPY is abundant in cerebral cortex, hippocampus, thalamus, hypothalamus and brainstem.¹¹) It has been suggested that the highest concentration of NPY neurones are found in the hypothalamic and ventrolateral medullary area. Although the exact function of NPY in the brain is not fully understood, it plays a major role in feeding, behaviour¹²) and sympathetic modulation (presyn-

aptic inhibition).¹³) In the periphery, NPY is found in the peripheral nerves and the circulation. It is present in most sympathetic nerve fibers, particularly in the dense plexuses around the blood vessels. Since vasoconstriction is the major net effect of NPY observed peripherally,¹⁴) over the past few years, much advancement in the study of the NPY receptors has been achieved. The possibility of NPY-related pharmaceutical agents, particularly for cardiovascular diseases has been raised considerably. Therefore, it is necessary to have some understanding of NPY receptors.

Initially two subtypes of NPY receptors were proposed on the basis of the affinity of the 13–36 fragment of NPY and they were named as Y1 and Y2 receptor.¹⁵) The Y1 receptor required the whole NPY or PYY molecule for activation whereas Y2 was selectively stimulated by the long C-terminal NPY or PYY fragments. It was, however, subsequently clear that some actions of NPY could not be performed by PYY and a third receptor subtype — the Y3 receptor was proposed.¹⁶) This receptor is believed to be exclusively NPY-responsiveness and is detected in the brain stem, heart and adrenal medulla. To date, however, two other NPY receptors Y4 and Y5 have been characterized. While Y5 receptors have raised considerable interest as a mediator of NPY stimulated food intake; additional NPY receptor subtypes with various target organ actions may become available in the near future.^{17,18})

The Y1 receptor is post junctional at the vascular sympathetic neuroeffector junction and is the best-characterized receptor so far for NPY. The receptor has been cloned.¹⁹) It is generally considered that the increase in blood pressure following NPY administration is mediated by the Y1 receptor. In fact, Y1 receptor agonists are as effective as NPY or PYY in producing the same effect. The vasoconstriction appears to depend on the availability and influx of extracellular Ca²⁺ as this response is blocked by L-type calcium channel blockers.²⁰) It may be pointed out that NPY is also a powerful potentiator of norepinephrine-evoked vasoconstriction. Therefore, in the periphery, NPY is capable of acting postsynaptically either through its direct vasoconstriction effect or through an indirect potentiation of vasoconstrictor agents like norepinephrine. The exact role of the Y1 receptor in the brain is not known. It has been shown that Y1 receptors mediate some interesting effects in several behavioral models including feeding behaviour, anxiolysis etc.

In brain, however, Y2 receptors predominate

over the Y1 type raising the possibility that Y2 receptor function is different in the central nervous system. In fact, stimulation of Y2 receptors by NPY agonists has been shown to have vasodepressor response.²¹⁾ This effect is mediated by what is termed as “presynaptic inhibition of norepinephrine release”. In other words, norepinephrine release is decreased by the stimulation of Y2 receptors in the brain. In the periphery, Y2 receptors are also found in the prejunctional sites mainly at the sympathetic neuroeffector junction. Y2 receptors in the periphery may be involved in what is called as “fine tuning of norepinephrine release” and is involved in inhibition of transmitter release.

Although numerous reports have now confirmed the existence of Y3 receptors in periphery (cardiac membrane, adrenal medulla) and brain (nucleus tractus solitarius), their role is not well defined yet.²²⁾ It has been suggested that the inhibitory response of Y3 receptor stimulation is related to suppression of adenylate cyclase activity and is linked to a pertussis toxin-sensitive G protein.²²⁾ These data are interpreted to mean that the role of NPY seems to be much more complicated than initially believed, particularly when one considers the interactions between the peptides and the three types of receptors.

NPY and Congestive Heart Failure

Within the brain, norepinephrine and NPY are coexisting in high densities in the paraventricular nucleus and the arcuate nucleus. It is reasonable to assume that by studying the interaction of norepinephrine and NPY at these areas, one could gain an insight into the pathophysiology of heightened sympathetic drive. Basu *et al.*²³⁾ using a Microdialysis method, investigated paraventricular nucleus in congestive heart failure following myocardial infarction. The aim of the study was to analyze the possible effects that NPY might have on the release of norepinephrine from paraventricular nucleus in experimental animals. Norepinephrine level was higher in paraventricular nucleus of congestive heart failure (Table 1). When NPY was infused to the paraventricular nucleus in control animals, the norepinephrine secretion was reduced to more than 50% (Table 2). However, there was no significant decrease observed in the secretory rate of norepinephrine from paraventricular nucleus in animals undergoing congestive heart failure (Table 2). Since NPY is a well known presynaptic inhibitor of norepinephrine release, these data may indicate that congestive heart failure may be associated with the defect of

Table 1. Baseline Norepinephrine Levels in the Paraventricular Nucleus

	Norepinephrine levels (pg./ul)
Control	53 ± 7
Congestive heart failure	654 ± 20*

The values are means ±S.E. of 4 experiments. Baseline samples were collected 2 h after implantation of the microdialysis probe. Congestive heart failure was produced by coronary ligation in the rats (8 to 12 weeks following surgery). * $p < 0.05$.

Table 2. Effect of NPY (10^{-8} M) on the Release of Norepinephrine in the Paraventricular Nucleus

	Norepinephrine levels (percent change from pre-drug levels)
Control	-56 ± 5
Congestive heart failure	-22 ± 4*

The values are means ±S.E. of 4 experiments. Norepinephrine release is expressed as the percent change from the pre-drug baseline levels. In other words, NPY was able to inhibit norepinephrine release more in the control and less in congestive heart failure. * $p < 0.05$.

Y2 receptors in the brain. The cause of this decreased responsiveness of paraventricular nucleus to the inhibitory effect of NPY in congestive heart failure is not known at this stage, however, it is reasonable to believe that heightened sympathetic activity may be precipitated due to a defect in the NPY receptor (Y2) in congestive heart failure. The total number of receptors were also decreased. Spontaneously hypertensive and aortic-banded rats,²⁴⁾ showing increased sympathetic tone have similar defects in NPY modulation.

Peripherally, vasoconstriction is the hallmark in congestive heart failure. Although, various investigators have shown that plasma norepinephrine is clearly implicated here, the role of NPY can not be underestimated in this process. In fact, it is quite possible that alterations in concentration and activity of NPY could be implicated in the clinical picture as it plays an important role as a neuromodulator for attaining a normal sympathetic activity both centrally and peripherally under physiological situations. The possible changes in NPY concentration/function, therefore, could be the cause or effect of the heightened sympathetic drive in congestive heart failure. As indicated earlier, it is now well known that the activation of this powerful system is not at all beneficial to patients with heart failure. Peripherally, over activity of postsynaptic receptors (Y1) may

lead to vasoconstriction, increased ventricular afterload and a greater workload on the myocardium. Whether or not NPY is more involved in the potentiation of norepinephrine function, however, remains an issue, which needs further investigation.

Future Therapeutic Target

The discovery of NPY has opened an exciting prospect of a new direction in the therapy of congestive heart failure. NPY comes with a great potential for effective pharmacological manipulation producing a safe and powerful sympathomodulatory agents. First, it is colocalized with norepinephrine influencing their release (Y2 receptor mediated effect). Secondly, it is co-released with norepinephrine and interacts extensively in addition to acting on its own postsynaptic receptor (Y1 receptor mediated effect). Finally, being an endogenous substance, it has a great advantage as a therapeutic target over many others. Although many agonists and antagonists of NPY have been tried in the recent past, their efficacy in cardiologic diseased states is poorly known. It is expected that the beginning of the 21st century will see better drugs directed towards NPY receptors (agonists and /or antagonists) in congestive heart failure.

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