[ISSN:2582-3663]

Canadian Journal of Biomedical Research and Technology

**Can J Biomed Res & Tech**

February 2020 Vol:2, Issue:5



# A Review on Heart-Neurohypophysis Functional Axis and its Importance In Cardiovascular Diseases

**Open Access** **Review Article**

**Paolo Lissoni[1]*, Arianna Lissoni[2], Giusy Messina[3], Francesco Pellizzoni[4], Giuseppe Di Fede[5]**

Institute of Biological Medicine, Milan, Italy

***Address for Correspondence**

Paolo Lissoni, Institute of Biological Medicine, Milan, Italy

**Submission:** February 07, 2020
**Published:** February 20, 2020



## Abstract

Until few years ago, the cardiac function was considered to be regulated only by hemodynamic parameters, and by the sympathetic and parasympathetic nervous systems. On the contrary, the recent advances in the knowledge of neuroendocrine and neuroimmune interactions achieved by the new medical specialization of the Psychoneuro endocrinoimmunology (PNEI) have demonstrated that the various activities of the heart, including its endocrine function, are also under a neuroendocrine and immune regulation, as well as on the other side that the heart may influence both neuroendocrine and immune cytokine secretions, namely through a preferential production of ANP or ET-1. Therefore, the possibility to modulate the cardiac functions by acting on its neuroendocrine and cytokine-mediated immune regulation, may constitute a new therapeutic strategy in the treatment of the cardiovascular diseases.

**Keywords:** Anti-diuretic hormone (ADH); Atrial natriuretic peptide (ANP); Cardiovascular diseases; Endothelin-1 (ET-1); Melatonin; Neurohypophysis; Pineal gland

## Introduction

The heart is physiologically under two different central neuroendocrine regulations played by brain opioid system-hypothalamus-pituitary axis and by the pineal gland through its connections with the brain cannabinergic system, which are active in stress conditions or in pleasure and spirituality states, respectively *[1-3]*. Moreover, within the pituitary gland, two different regulatory mechanisms on the cardiac functions have to be identified, consisting of adeno-hypophysis, namely involved in the modulation of cardiac tissue growth and metabolic functions, and neurohypophysis, which plays a fundamental role in the regulation of fluid mass by controlling the metabolism of water. Therefore, it is possible to identify the existence of a cardiac-neurohypohyseal endocrine axis, which is due to the interactions between the two hormones released from the neurohypophysis, the antidiuretic hormone (ADH) and oxytocin, and the two main endocrine molecules produced by the heart, the atrial natriuretic peptide (ANP) and endothelin-1 (ET 1), mainly secreted by cardiomiocytes of atrial right and by the endocardium endothelium and most genera by the overall endothelial cells, respectively *[4,5]*. Moreover, the Neurohypophysis is under a further neuroendocrine regulation, namely exerted by the brain opioid and cannabinergic systems and the pineal gland *[6-8]*. The most investigated pineal hormone is the indole melatonin (MLT), which presents a physiological light/dark circadian rhythm, with a low production during the light period and a maximal secretion during the dark phase of the day *[9]*. MLT has been proven to interact with the heart endocrine activity by influencing the secretion of both ANP and ET-1 *[10]*. Therefore, heart, neurohypophysis and pineal gland would constitute a fundamental functional axis in the control of fluid mass and water metabolism. Then, the investigation of heart-neurohypophysis and heart-pineal relationships in a separate way does not permit to completely understand the physiology of the neuroendocrine regulation of heart endocrine activity. Moreover, in addition to the well documented neuroendocrine regulation, the cardiac endocrine and metabolic functions have been seen to be also under an immune cytokine regulation *[11]*, as confirmed by the evidence of cardiac receptors for cytokines, namely for the inflammatory cytokines IL-6 and TNF-alpha, whose secretion is stimulated by ET-1 *[5]* and inhibited by ANP *[4]*. More in detail, both TNF-alpha and IL-6, as well as IL-17 and IL-18 have appeared to reduce the cardiac miocyte contractility, and activate heart tissue remodelling. At the end stages of heart failure, the inflammatory cytokines have been proven to be directly produced by the same miocardial cells. Therefore, heart failure progression would not depend only on mechanicistic hemodynamic variables, but also on the biological response in terms of both neuroendocrine and immune cytokine behaviour. Then, because of the detrimental effects of the inflammatory cytokine on cardiac function, the control of cytokine secretions would play a fundamental role in counteracting the evolution of the various cardiovascular diseases.

## Heart-Neurohypophysis Interactions

Irrespectively of the degree of heart failure, the neurohypophyseal response in terms of ADH secretion may be inadequate and excessive with respect to the status of the

cardiac function and allows an exaggerated fluid retention as a consequence of a possible altered neuroendocrine regulation of the neurohypophyseal activity and endocrine cardiac profile. In addition to its stimulatory effect on the activation of the renin-angiotensin II-aldosteron system (RAA), ADH has been proven to stimulate ET-1 secretion, which also stimulates ADH secretion *[12]*. On the contrary, oxytocin stimulates ANP secretion and is stimulated by ANP *[13,14]*. Therefore, heart and neurohypophysis would be connected by two positive feed-back systems, represented by ANP-oxytocin and ET-1-ADH axis systems. The relation between these two endocrine circuits is founded on a negative feed-back mechanism, since ANP has been proven to inhibit ET-1 secretion, whereas ET-1 may stimulate ANP release *[4,5,14]*. ET-1 secretion and activity may be also inhibited by estrogens *[15]* and by anti-phosphodiesterase (PDE), because of the stimulatory action of PDE agents on ET-1 secretion *[16,17]*. Finally, the neurohypophyseal activity is under a regulatory control played by suprahypothalamic brain areas with several and complex neuronal interactions, with, however, two fundamental brain interneuronal systems, consisting of brain opioid and cannabinoid systems. ADH secretion is stimulated by the mu-opioid agonists *[18]* and inhibited by the cannabinoids *[19]*. Since brain opioid system is active in stress conditions and in depression *[6]*, stress-and depression-induced changes in body weight due to fluid retention could depend on alterations in brain neuroendocrine control of ADH secretion.

## Heart-Pineal Gland Interactions

Heart secretion of ANP is connected with the pineal gland by a reciprocal stimulatory relation, since ANP has been proven to stimulate MLT secretion from the pineal gland *[20]*, and in a reciprocal manner MLT may promote ANP secretion by the cardiac miocytes *[10]*. MLT has also been proven to inhibit ET-1 secretion *[10]*. Then, the pineal gland and the heart would be linked by two types of feed-back mechanisms, a positive feed-back mechanism between MLT and ANP and a negative feed-back circuit between MLT and ET-1. On the contrary, most controversial are the results concerning the relation between pineal gland and neurohypophysis. However, ADH would seem to stimulate MLT secretion *[21,22]*, while MLT would exert a prevalent inhibitory action on ADH secretion, according to a negative feed back mechanism. The relations occurring among heart, pineal gland and neurohypophysis are illustrated in Figure 1.

## Heart Endocrine Activity and Cardiovascular Diseases

ET-1 blood concentrations have appeared to be abnormally high in most cardiovascular diseases, including hypertension, pulmonary hypertension, myocardial infarction and atherosclerosis. Moreover, in particular the progressive increase in ET-1 blood levels would constitute one of the most adequate clinical parameters to monitor the evolution into heart failure. Because of its vasoconstrictor effect and its capacity of inducing endothelial damages and cardiac hypertrophy, ET-1 would be involved in the pathogenesis of most cardiovascular diseases, including hypertension, heart failure and cardiac ischemic diseases *[23]*. In particular, the evidence of abnormally high levels of ET-1 has appeared to be associated with a worse prognosis in the miocardial infarction *[23]*. This would depend on the fact that ET-1-induced stimulation of inflammatory cytokines would further enhance miocardial tissue ischemic damage. Therefore, because of the pathogenetic role of ET-1, each condition which allows an enhanced ET-1 secretion has to be considered as a risk factor for the cardiovascular diseases and their severity. In particular, an enhanced brain opioid system activity, as well as in stress conditions or in depression *[6]*, or a deficiency in the pineal gland may allow to an enhanced secretion of ET-1. These findings could explain the more severity of heart failure in depressed patients and the relation between cardiac ischemic disease and reduced pineal endocrine function *[24,25]*. On the contrary, in experimental conditions it has been demonstrated that MLT therapy may reduced tissue damage induced by the miocardial infarction *[10]*, and this effect would be due at least in part to MLT-induced stimulation of ANP secretion. ADH and ANP blood levels have also appeared to be high in heart failure, with, however, different clinical significance, since the high levels of both ET-1 and ADH would be responsible for the progression of disease, whereas the enhanced ANP secretion would be the expression of a compensatory mechanism to counteract ADH-induced fluid retention and ET-1- induced endothelial damage. By summarizing, the prognosis of the myocardial infarction has been proven to be worse in the presence of abnormally high levels of ET-1, IL-6, TNF-alpha, IL-17, IL-6 *[26]* and low concentrations of ANP and MLT. ANP-to-ET-1 ratio could constitute a simple clinical index to evaluating the interactions occurring between ANP and ET-1 secretion by the heart, which would influence the prognosis of the cardiovascular diseases, because of the detrimental activity of ET-1 and the biological benefits determined by ANP. In addition to its vascular and diuretic effects, ANP may also play metabolic and immune effects *[4]*, namely consisting of the inhibition of leptin release from adipocytes *[27]* and the macrophage secretion of inflammatory cytokines, including TNF-alpha and IL-6 *[24]*. The evidence of high blood levels of ANP has been shown to be associated with a better prognosis in both septic shock and miocardial infarction, and this finding would depend at least in part on ANP-induced prevention of a possible exaggerated production of inflammatory cytokines, which may further amplify both sepsis-related vasodilatation and the ischemic tissue damage *[26]*. Finally ANP plays also an anti-arrhythmic activity and atrial fibrillation would be due at least in part to an ANP deficiency *[4]*.

## Neuroendocrine Therapy of Heart Function

Since it has been well documented that the clinical history of cardiac ischemic disease, heart failure and most cardiovascular pathologies may depend also on the biological immunoinflammatory response of patients, mainly consisting of monocyte- and macrophage-induced production of inflammatory cytokines *[26,28]*, a neuroendocrine strategy performed to control the cytokine network and the endocrine activity of the heart, could represent a new possible way in the

treatment of the cardiovascular diseases. In more detail, there are two fundamental monocyte subsets depending on the expression of the only CD14 or both CD14 and CD16 markers. CD16 negative monocytes would exert a pro-inflammatory activity, whereas CD16-positive monocytes have appeared to play anti-inflammatory and immunosuppressive effects. The macrophage-mediated secretion of inflammatory cytokines, including IL-6 and TNF-alpha, is stimulated by ET-1 *[5]* and inhibited by ANP *[4]*. ET-1 would stimulate the macrophage system and inhibit T lymphocyte system, whereas in contrast ANP would stimulate T cell differentiation and proliferation and inhibit the macrophage functions. Then, ANP analogues could be therapeutically employed to regulate both cardiac function and immune cytokine network, as a neuroendocrine and immune modulating molecule. MLT could also successfully be used to stimulate ANP and inhibit ET-1 secretions *[10]*. Finally, cannabinoids agonists may be employed to inhibit IL-17 secretion from TH17 lymphocytes *[29]*, which may also negatively influence the cardiac function, as well as to counteract the atherosclerotic progression *[30]*.

## Conclusions

The possibility to influence the neurohypophyseal activity by a neuroendocrine approach may allow to a better control of heart failure-related fluid retention, as well as the same cardiac ischemic disease because of the stimulatory role of ADH on ET-I secretion, which would constitute the main agent responsible for both cardiac ischemia and cardiac hypertrophy. Then, the future of Cardiology could substantially consist of the neuroendocrine modulation of the mechanisms involved in the control of heart endocrine functionless by acting on the main hormones involved in the control of fluid mass and water metabolism, including ANP, ET-1 and ADH, which have been proven to also exert immunomodulatory effect *[4,5,29]*.

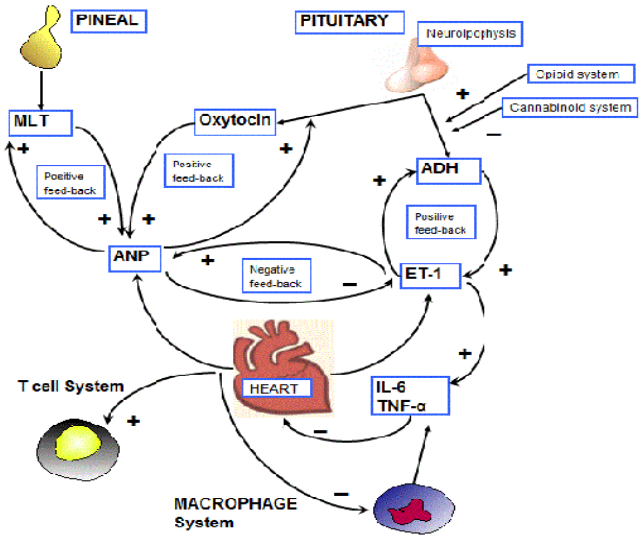


**Figure 1:** Neuroendocrine regulation of heart endocrine activity

## References

1. Rubinow DR (1987) Brain, Behaviour and Immunity: An interactive system. I Nati Cancer lnst Monogr 10: 79-82.
2. Lissoni P, Resentini M, Mauri R, Esposti D, Esposti G, et al., (1986) Effects of Tetrahydrocannabinol on Melatonin Secretion in Man. Horm Metab Res 18: 77-78.
3. Manfredi B, Sacerdote P, Bianchi M, Locatelli L, Veljic-Radulovic J, et al., (1993) Evidence for an Opioid Inhibitory Tone on T cell Proliferation. J Neuroimmunol 44: 43-48.
4. De Vito P (2014) Atrial Natriuretic Peptide: An Hold Hormone, or a New Cytokine? Peptides 58: 108-116.
5. Grant K, Loizidou M, Taylor I (2003) Endothelin-1: A Multifunctional Molecule in Cancer. Br J Cancer 88: 163-166.
6. Lewis JW, Shavit Y, Terman GV, Nelson LR, Gale RP, et al., (1983) Apparent Involvement of Opioid Peptides In Stress-Induced Enhancement of Tumor Growth. Peptides 4: 635-638.
7. Maestroni GJM (1993) The Immunoneuroendocrine Role of Melatonin. J Pineal Res 14: 1-10.
8. Lissoni P (1999) The Pineal Gland as a Central Regulator of Cytokine Network. Neuro Endocrinol Lett 20: 343-349.
9. Brzezinski A (1997) Melatonin in Humans. N EngI J Med 336: 186-195.
10. Sallinen P, Manttari, Leskinen FI, Vakkuri O, Ruskoaho H, et al., (2008) Long-Term Postinfarction Melatonin Administration Alters The Expression of DHPR, RyR2, SERCA2, and MT2, and elevates ANP Level in the Rat Left Ventricle. I Pineal Res 45: 61-69.
11. Idzkowska E, Eljasewicz A, Miklasz P, Musiai WI, Tycinska AM, et al., (2015) The Role of Different Monocyte Subsets In The Pathogenesis of Atherosclerosis and Acute Coronary Syndromes. Scand J Immunol 82: 163-173.
12. Yamamoto T, Kimura T, Ota K, Shoji M, Inoue M, et al., (1992) Central Effects of Endothelin-1 On Vasopressin Release, Blood Pressure, and Renal Solute Excretion. Am J Physiol 262: 856-862.
13. Haanwinckez MA, Elias LK, Pavaretto AL, Gutkowska I, McCann SM, et al., (1995) Oxytocin Mediates Atrial Natriuretic Peptide Release and Natriuresis After Volume Expansion in The Rat. Proc Am Acad Sci USA 92: 7902-7906.
14. Evrard A, Hober C, Racadat A, Lefevre I, Wantyghem MC (1999) Atrial Natriuretic Hormone and Endocrine Functions. Ann Biol Clin (Paris) 57: 149-155.
15. Jankowski M, Rachelska G, Donghao W, McCann SM, Gutkowska I (2001) Estrogens Receptors Activate Atrial Natriuretic Peptide in The Rat Heart. Proc Am Acad Sci USA 98: 11765-11770.
16. Heid HD, Wendel A, Uhling (1997) Phosphodiesterase Inhibitors Prevent Endothelin-1-Induced Vasoconstriction, Bronchoconstriction, and Thromboxane Release in Perfused Rat Lung. Biochem Biophys Res Comm 231: 22-25.
17. Zhou Z, de Beer VJ, Bender SB, Jan Danser AH, Merkus D, et al., (2014) Phosphodiesterase-5 Activity Exerts

Coronary Vasoconstrictor Influence in Awake Swine, That is Mediated in Part Via An Increase in Endothelin Production. Am J Physiol Reart Circ Physiol 306: 918-927.

18. Korinek AM, Languille M, Bonnet E, Thibonnier M, Sasano P, et al., (1985) Effect of Postoperative Extradural Morphine on ADH Secretion. Br J Anaesth 57: 407-411.
19. Luce V, Fernandez-Solon J, Rettori V, de Laurentis A (2014) The Inhibitory Effect of Anandamide on Oxytocin and Vasopressin Secretion from Neurohypophysis Mediated by Nitric Oxide. Regul Pept 188: 31-239.
20. Lissoni P, Pellizzoni F, Grugni G, Guzzaloni G, Mauri R, Archili C, et al., (1990) Melatonin Response to Atrial Natriuretic Peptide Administration in Healthy Volunteers. J Cardiovasc Pharmacol 16: 850-852.
21. Bojanowska E, Forsling ML (1997) The Effects of Melatonin on Vasopressin Secretion In-Vivo: Interactions with Acetylcholine and Prostaglandins. Brain Bull Res 42: 4578-4601.
22. Juszczak M, Boczek-Leszcyk E, Stempniak B (2007) Effect of Melatonin on The Vasopressin Secretion as Influenced by Tackykinin NK-1 Receptor Agonist and Antagonist In-Vivo and In-Vitro. J Physiol Pharmacol 58: 829-843.
23. Bras-Silva C, Lweite-Moreira AF (2008) Myocardial Effects of Endothelin-1. Rev Port Cardiol 27: 925-951.
24. Domininguez-Rodriguez A, Abreu-Gonzales P, Garcia-Gonzalez M, Reiter RJ (2006) Prognostic Values of Nocturnal Melatonin Levels as a Novel Marker in Patients with ST-Segment Elevation Miocardial Infarction. Am J Cardiol 97: 1162-1164.
25. Kent LK, Shapiro PA (2009) Depression and Related Psychological Factors in Heart Disease. Harv Rev Psychiatry 17: 377-388.
26. Ji H, Li Y, Fan Z, Zuo B, Jian X, et al., (2017) Monocyte/Lymphocyte Ratio Predicts The Severity of Coronary Heart Disease: A Syntax Score Assessment. BMC Cardiovascular Disord 17: 90.
27. Moro C, Klimcakova E, Lolmede K, Berlan M, Lafontain M, et al., (2007) Atrial Natriuretic Peptide Inhibits The Production of Adipokines, and Cytokines Linked to Inflammation and Insuline Resistance in Human Subcutaneous Adipose Tissue. Diabetologica 50: 1038-1047.
28. Johnson HM, Torres BA (1985) Regulation of Lymphokine Production by Arginine Vasopressin and oxytocin: Modulation of Lymphocyte Function by Neurohypophyseal Hormones. J Immunol 135: 7783-77855.
29. Grotehnermen F (2004) Pharmacology of Cannabinoids. Neuro Endocrinol Lett 25: 14-23.
30. Steffens S, Veillard NR, Arnaud C, Pelli G, Burger F, et al., (2005) Low-Dose Oral Cannabinoid Therapy Reduces Progression of Atherosclerosis. Nature 434: 782-786.