SUNTEXT REVIEWS

SunText Review of Pediatric Care
ISSN: 2766-5216

Open Access
Review Article
Volume 1:2

High Homocysteine Levels or Low Nocturnal Production of the Pineal Hormone Melatonin as a Possible Alteration Responsible for Most Human Diseases? This Is The Question

Lissoni P*, Di Fede G and Messina G

Institute of Biological Medicine, Milan, Italy

***Corresponding author:** Lissoni P, Institute of Biological Medicine, Milan, Italy; E-mail: paolo.lissoni@gmx.com

Received date: 20 December 2020; **Accepted date:** 27 December 2020; **Published date:** 31 December 2020

Citation: Lissoni P, Di Fede G, Messina G (2020). High Homocysteine Levels or Low Nocturnal Production of the Pineal Hormone Melatonin as a Possible Alteration Responsible for Most Human Diseases? This Is The Question. SunText Rev Pediatr Care 1(2): 112.

DOI: https://doi.org/10.51737/2766-5216.2020.012

Abstract

Is it possible to identify a biological alterations occurring in the overall systemic human diseases? Generally, most biomarkers are in relation to only a few number of similar pathologies, whereas two main alterations have been described in the most important human pathologies, including hypertension, brain and cardiac ischemic disorders, tumors, and neuropsychiatric diseases, consisting of an enhanced production of homocysteine (HCY) and a diminished nocturnal production of the pineal hormone melatonin (MLT). However, these two alterations would be characterized by opposite biological effects, since MLT has been proven to protect cardiovascular and nervous functions, whereas HCY and its metabolites may be toxic for several tissues, by predisposing to metabolic, nervous, and cardiovascular diseases. Therefore, the question to be solved is to establish which relation may exist between hyper-production of HCY and diminished secretion of MLT. According to the results available in the literature, since it has been shown that MLT may counteract HCY production and activity, it is possible to conclude that the primary alteration is consisting of an age-dependent diminished pineal function, whereas the enhanced HCY production would simply represent the consequence of the diminished pineal endocrine activity.

Keywords: Homocysteine; Melatonin; Methionine; Pineal gland; Systemic diseases

Introduction

Each human local or systemic disease is characterized by alterations involving some clinical parameters, which, however, may represent the specific cause of disease, or the simple consequential effect of the pathogenesis of disease. In some cases, it is easy to distinguish the cause of disease from its effects, as occurring in the diabetes, whose consequence is consisting of the increase in glucose blood levels, but whose cause is the diminished insulin production, or an enhanced insulin resistance. On the contrary, in some other cases, it is more difficult to clinically distinguish the cause of disease from its effects by the simple laboratory analyses. This is the case of the evidence of hyper-homocysteinemia in most human systemic diseases, consisting of the presence of abnormally high blood levels of homocysteine (HCY) [1-5]. At present, however, despite the evidence of an association between increase blood concentrations of HCY with several human systemic diseases [1-5], it remains to be established whether the increased levels of HCY may represent the causative factor, or the simple effect of other biological alterations, as confirmed by the fact that the correction of the hyper-homocysteinemia does not allow a concomitant reduction in the incidence of hyper-homocysteinemia supposed related-pathologies [6]. From a physiopathological point of view, the great number of biomarkers could be sub-divided into three main subtypes, represented by disease-specific markers, biological response markers, and disease mechanism-related markers. Most biomarkers regard single specific diseases, or a few number of similar diseases. Biological response markers include several systemic diseases, but they simply reflect the effects of the systemic pathology, as in the case of the inflammatory status, which may be clinically documented by several marekers, including CRP, ESR, neopterin, and soluble IL-2 receptors [7]. On the contrary, some other biomarkers also provided by a general significance are ill relation not only to the effects of some diseases, but the mechanisms responsible for the cause of disease itself. According to the great number of opinions or hypotheses

reported in the literature, it is possible to identify two main altered clinical parameters, which have been proposed as the cause of most human systemic pathologies, consisting of the enhanced production of HCY with a following condition of hyper-homocysteinemia [1-5], and the diminished production of the pineal indole hormone melatonin (MLT), particularly during the night, with a consequent loss of its physiological light/dark circadian rhythm [8]. These different conditions could represent two independent pathogenetic factors, or alternatively they could be connected by a cause/effect ratio, but in this case it would have to be established which is the cause, and which is the effect. To solve this question, obviously firstly we have to analyze which is in details the biological activities of both HCY and MLT, in any case by constantly taking into consideration their opposite effects, since while MLT has been proven to protect against most human systemic pathologies [8-10], HCY would promote their development [1-5], with two consequent opposite therapeutic strategies, consisting of enhancing MLT blood levels and decreasing those of HCY.

Biology and Clinical Significance of Homocysteine

HCY is a sulfur containing aminoacid, which is produced during the metabolism of the aminoacid methionine (MT) to cysteine (CYS). MET is the unique source of HCY, which may undergo three different metabolic pathways, to reform MET, to be metabolized to CYS, or to be cyclized to form homocysteinethiolactone (HTL), which would constitute the main toxic intermediate of HCY [11]. The increase in HCY blood concentrations, which are generally less than 12 micromol/L, may be induced by several causes, including a defective metabolism of MET due to gene mutations, vitamins deficiencies, namely those of folic acid, B6 and B12, high consumption of meat, and deficiency of cystathionine-beta synthase, which is involved in the production of hydrogen sulfide (H2S), a lipid-soluble gaseous molecule [12], and which has been proven to play a hypotensive action, to promote brain development, and to decrease the neuronal excitability. A diminished endothelial production of H2S would play a role in the pathogenesis of the hypertension. Moreover, the toxicity related to a condition of hyper-homocysteinemia would depend at least in part on the concomitant presence of a demised H2S endogenous production [12]. HCY has appeared to stimulate the endothelial production of inflammatory cytokines, as well as the expression of some vascular cell adhesion molecules, with a following increased monocyte adhesion to the arterial endothelium, which may contribute to the development of the atherosclerotic processes by facilitating the monocyte-macrophage infiltration into the arterial wall [12]. Moreover, HCY may induce tissue damage by causing an oxidative stress leading to oxidation of low density lipoproteins (LDL), which also contribute to the atherosclerotic pathogenesis. Finally, an altered HCY metabolism may allow the production of S-nitroso-homocysteine, which induces endothelial dysfunction and inhibition of the vasodilatory action of nitric oxide (NO).

Homocysteine-Related Diseases

Hyper-cysteinemia has been proven to be an independent risk factor for atherosclerosis [1], cardiac and brain ischemic disorders [1], neurodegenerative pathologies [2], neoplasms [3], osteoporosis [4], and insuline resistance [5]. HCY may predispose to the neurodegenerative diseases by enhancing the oxidative stress [2,11], and to osteoporosis by stimulating the osteoclastic activity [4]. On the contrary, the relation between HCY production and tumor development is more complex, since it has been shown that proliferating tumor cells may produce and release HCY [3]. Then, cancer-related hyper-homocysteinemia would constitute a marker of tumor growth, biological malignancy, and extension, rather than a causative factor for tumor onset [3]. The hyper-homocysteinemia may be treated by supplementation with folic acid, B12 and B6 vitamins [6,11], but the control of hyper-homocysteinemia does not guarantee the control of hyper-homocysteinemia-related pathology.

Physiology of the Pineal Gland and Its Main Hormone Melatonin

The pineal gland is a neuroendocrine organ, which acts as a neurochemical transducer, by representing the only structure of human body able to modulate the whole biological systems in relation to the universal energetic conditions, namely the light/dark rhythm [8], through the circadian secretion of several indole and beta-carboline hormones, the most known of them is MLT. The light inhibits, whereas the dark stimulates MLT secretion from the pineal gland. Then, the evidence of a normal light/dark rhythm of MLT secretion, with higher levels during the night and lower concentrations during the day, would constitute a fundamental clinical parameter of the status of health. The main stimulus for MLT secretion is represented by beta-adrenergic receptor agonists [8], but MLT release is also stimulated by alpha-1 agonists, alpha-2 antagonists [8], mu-opioid agonists [13], cannabinoid agents [14], oxytocin [15], and the cardiac hormone atrial natriuretic peptide (ANP) [16], whereas it is inhibited by beta-blockers and alpha-2 agonists [8]. The main mechanism, which may explain the great number of biological effects played by MLT, including anticancer cytotoxic activity, immunostimulatory action, modulation of blood pressure in a hypotensive way, and cardio-neuroprotective properties [8] may be simply explained on the basis of the ability of MLT to modulate DNA expression [8].

Melatonin and Human Diseases

A diminished MLT secretion with a progressive loss of its physiological light/dark rhythm has been observed in most human systemic diseases, including depression, autism, schizofrenia [8], autoimmune diseases [17], essential hypertension [18], brain and cardiac ischemic disorders [19,20], and namely in tumors [8,21], by representing the main cancer-related endocrine deficiency. Because of its well documented cytotoxic antiproliferative action [8], and immunostimulatory activity on the anticancer immunity [21], cancer progression-related MLT deficiency would not simply represent an epiphenomenon, but it would be responsible at least in part for cancer growth and diffusion themselves.

Homocysteine-Melatonin Relationships

The question is to identify a possible connection between the decreased MLT secretion and enhanced HCY production, which have been described in the main human systemic pathologies. Unfortunately, no study has been performed up to now to concomitantly evaluate MLT and HCY blood concentrations. Then, at present it is possible only to elaborate some hypotheses on the basis of the biological properties of MLT and HCY. Some preliminary experimental studies have shown that MLT may inhibit HCY activity and production (22). Then, because of the potential inhibitory action of MLT on HCY secretion and toxicity, it is probable that the systemic disease-associated enhanced production of HCY may simply depends on the concomitant decline in MLT secretion, also reported in the literature in the same pathologies [17-21]. Moreover, MLT could reduce HCY levels, whereas HCY cannot replace MLT deficiency. Then, it is possible to suggest that MLT deficiency may precede and determine the abnormal production of HCY.

Conclusions

The most important human severe systemic diseases, including cancer, brain and cardiac ischemia, neuropsychiatric pathologies, and essential hypertension, have appeared to be characterized by two major constant alterations, consisting of enhanced HCY production and diminished nocturnal secretion of the pineal hormone MLT. Then,the question is to establish which causative connection may exist between these two fundamental biological systemic alterations. However, since MLT has been proven to counteract HCY activity and production [22,23], it is probable that the primary alteration is consisting of the progressive decline in pineal function and MLT secretion, as physiologically occurring with the age [8], while the increase in HCY levels may simply represent the consequence of a diminished inhibitory effect of the pineal gland on HCY production. Then, MLT therapy could constitute a new possibile therapy of hyper-homocysteinemia [23].

References

1. McCully KS, Wilson RB. Homocysteine theory of atherosclerosis. Atherosclerosis. 1975; 22: 215-227.
2. Mattson MP, Shea TB. Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends Neurosci. 2003; 26: 137-146.
3. Sun CF, Haven TR, Wu TL, Tsao KC, Wu JT. Serum total homocysteine increases with the rapid proliferation rate of tumor cells and decline up on cell death: a potential new tumor marker. ClinChim Acta. 2002; 321: 55-62.
4. Vacek TP, Kalani A, Voor MJ, Tyagi SC, Tyagi N. The role of homocysteine in bone remodeling. Clin Chem Lab Med. 2013; 51: 579-590.
5. Li Y, Zhang H, Jiang C, Xu M, Pang Y, Feng J, et al. Hyper-homocysteinemia promotes insulin resistance by inducing endoplasmic reticulum stress in adipose tissue. J Biol Chem. 2013; 288: 9583-9592.
6. Smulders YM, Blom HJ. The homocysteine controversy. J Inherit MetabDis. 2011; 34: 93-99.
7. Mills CD. M1 and M2 macrophages: oracles of health and disease. Crit Rev Immunol. 2012; 32: 463-488.
8. Brzezinski A. Melatonin in humans. N Engl J Med. 1997; 336: 186-195.
9. Regelson W, Pierpaoli W. Melatonin: are discovered antitumor hormone? Cancer Invest. 1987; 5: 379-385.
10. Lissoni P. Is there a role for melatoninin supportive care? Supp Care Cancer. 2000; 10: 110-116.
11. Jakubowski H. Molecular basis of homocysteine toxicity in humans. Cell Mol Life Sci. 2004; 61: 470-487.
12. Zhou C, Tang X. Hydrogen sulfide and nervous system regulation. Chim Med J. 2011; 124: 3576-3582.
13. Esposti D, Esposti G, Lissoni P, Parravicini L, Fraschini F. Action of morphine on melatonin release in the rat. J Pineal Res. 1988; 5: 35-39.
14. Lissoni P, Resentini M, Mauri R, Esposti D, Esposti G, Rossi D, et al. Effects of tetrahydrocannabinol on melatonin secretion in man. Horm Metab Res. 1986; 18: 77-78.
15. Sharkey JT, Puttaramu R, Word RA, Olcese J. Melatonin synergizes with oxytocin to enhance contractility of human myometrial smooth muscle cells. J Clin Endocrinol Metab. 2009; 94: 421-427.
16. Lissoni P, Pelizzoni F, Grugni G, Guzzaloni G, Mauri O, Archili C, et al. Melatonin response to atrial natriuretic peptide administration in healthy volunteers. J Cardiol Pharmacol. 1990; 16: 850-852.
17. Lissoni P, Messina G, Tantarelli R, Lissoni A, Tantarelli O, Pellgrino G, et al. The psychoneuroimmunology of human immune-mediated systemic diseases, including cancer and autoimmune diseases. J Mol Oncol Res. 2017; 1: 7-13.
18. Grossman E. Should melatonin be used to lower blood pressure? Hypertens Res. 2013; 36: 682-683.
19. Bob P, Fedor-Freybergh F. Melatonin, consciousness, and traumatic stress. J Pineal Res. 2008; 44: 341-347.

Citation: Lissoni P, Di Fede G, Messina G (2020). High Homocysteine Levels or Low Nocturnal Production of the Pineal Hormone Melatonin as a Possible Alteration Responsible for Most Human Diseases? This Is The Question. SunText Rev Pediatr Care 1(2): 112.

20. Brugger P, Marktl W, Herold M. Impaired nocturnal secretiion of melatonin in coronary heart disease. Lancet. 1995; 345: 1408.
21. Maestroni GJM. The immunoneuroendocrine role of melatonin. 1993; J Pineal Res. 14: 1-10.
22. Osuna C, Reiter RJ, Garcia JJ, Karbownik M, Tan DX, Calvo RC, et al. Inhibitory effect of melatonin on homocysteine-induced lipid peroxidation in rat brain homogenates. Basic Clin Pharmacol Toxicol. 2002; 90: 32-37.
23. Aminzadeh A, Meharzadi S. Melatonin attenuates homocysteine-induced injury in human umbelical vein endothelial cells. Fund Clin Pharmacol. 2018; 32: 261-269.