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Review article

The potential physiological crosstalk and interrelationship between two sovereign endogenous amines, melatonin and homocysteine

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ABSTRACT

The antioxidant melatonin and the non-proteinogenic excitotoxic amino acid homocysteine (Hcy) are very distinct but related reciprocally to each other in their mode of action. The elevated Hcy level has been implicated in several disease pathologies ranging from cardio- and cerebro-vascular diseases to neurodegeneration owing largely to its free radical generating potency. Interestingly, melatonin administration potentially normalizes the elevated Hcy level, thereby protecting the cells from the undesired Hcy-induced excitotoxicity and cell death. However, the exact mechanism and between them remain obscure. Through literature survey we have found an indistinct but a vital link between melatonin and Hcy i.e., the existence of reciprocal regulation between them, and this aspect has been thoroughly described herein. In this review, we focus on all the possibilities of co-regulation of melatonin and Hcy at the level of their production and metabolism both in basal and in pathological conditions, and appraised the potential of melatonin in ameliorating homocysteinemia-induced cellular stresses. Also, we have summarized the differential mode of action of melatonin and Hcy on health and disease states.

Contents

1. Introduction

Two completely independent endogenous biogenic amines, melatonin and homocysteine (Hcy), play a very decisive role in maintaining cellular homeostasis [1,2]. Melatonin is a tryptophan-derived chemical messenger secreted mainly from the pineal gland [2,3]; while Hcy is a non-protein forming amino acid and belongs to thiol group of molecule, which is formed during the metabolism of methionine [1,4]. The sleep–

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wake cycle regulating hormone, melatonin [5,6], is not only well-known for its potent antioxidant properties [7,8], but has also been reported to play pivotal role in regulating endocrine rhythms [9,10], and ameliorating various neuro-pathological processes [11–13]. On the other hand, elevated plasma Hcy level (hyperhomocysteinemia, HHcy) has become the independent risk factor for cardiovascular disorders [14–15] and degenerative diseases [16–17]. Various reports state that Hcy is an excitotoxic molecule and also enhances oxidative as well as inflammatory stress, which ultimately results in apoptosis [18–20], and has been suggested as a putative marker of cellular oxidant status [21].

Although independent, melatonin and Hcy are reciprocally-related to each other in their mode of action and studies of the last decade have highlighted a causal link between the plasma levels of melatonin and Hcy [22–23]. It is evident that the level of Hcy increases in the elderly people, which is an indication of different pathological conditions during the process of aging as Hcy is highly excitotoxic [24–26]. On the contrary, production and secretion of melatonin decrease with progression of age, which has been linked with insomnia in the older population [27–28]. Interestingly, several reports provided evidences that melatonin controls the plasma Hcy level [22,29,30] and also protects the cells against HHcy-induced toxicities [18,31,32]. A substantial body of evidence has also speculated that Hcy may modulate plasma melatonin level, but the molecular mechanism remains undefined [33]. Based on the available literature, we have summarized all the states of health and disease in which melatonin and Hcy are implicated, and appraised the possibilities of how melatonin and Hcy are co-regulated in normal and pathological conditions.

2. Biosynthesis and regulation of melatonin

Melatonin which is synthesized by the pinealocytes of pineal gland contributed to its level in circulation [3,34]. While melatonin synthesis by gut, Harderian gland, thymus, bone marrow, skin, lymphocytes and photoreceptor cells of retina exerts an autocrine or paracrine role [2,35,36]. Tryptophan, the biological precursor of melatonin, is taken up from blood by the pinealocytes [37]. Tryptophan gets converted to 5-hydroxytryptamine (serotonin) which in turn produces melatonin via the ultimate precursor, N-acetylserotonin (NAS) [38,39]. In the biosynthesis of melatonin two enzymes play vital roles: arylalkylamine N-acetyltransferase (AANAT) catalyzes the penultimate reaction which is under circadian control and hydroxyindole-O-methyltransferase (HIOMT) produces melatonin from NAS (Fig. 1) [9,40,41]. The highly elevated levels of melatonin in mitochondria [41], along with predominant expression of AANAT in mitochondria [42,43] suggested that at organelle level mitochondria themselves produce melatonin [44].

Melatonin exerts physiological effects through its receptors: MT1 and MT2, which are expressed in various tissue types [45]. At least partially, the physiological effects of melatonin are mediated by binding to cytosolic enzyme quinone reductase 2 (MT3) and retinoid related orphan nuclear hormone receptor (RZR/RORα) [46,47]. Additionally, the free radical scavenging action of melatonin is receptor independent [48].

The secretion of melatonin is under circadian control with peak secretion at night, while its concentration during the day is low [49]. Apart from diurnal variation, melatonin level is also affected by changes

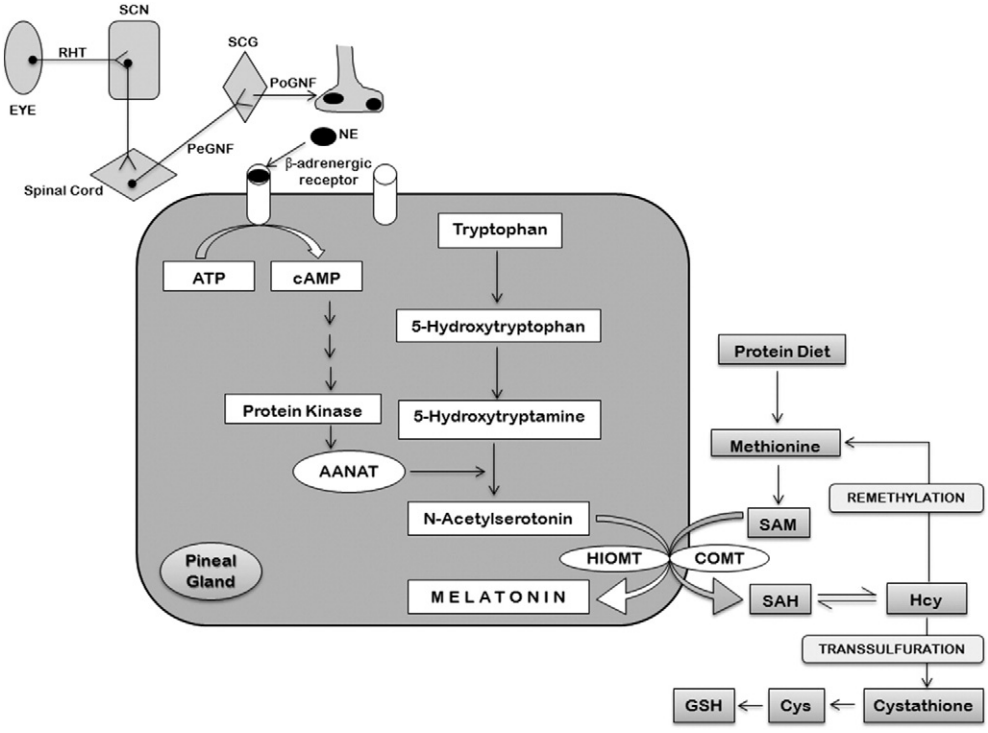

Fig. 1. Interlinking biosynthesis of melatonin and homocysteine (Hcy). The diurnal variation in melatonin synthesis is tightly regulated by a complex neuronal circuit and their secretions that ultimately stimulate the beta-adrenergic receptors of pineal gland acted upon by norepinephrine released from the postganglionic nerve fibers (PoGNF) synapse in superior cervical ganglia (SCG). The SCG receives input from the preganglionic nerve fibers (PeGNF) originating from spinal cord and the spinal cord is connected to the master regulatory center of melatonin synthesis, the suprachiasmatic nucleus (SCN). On the other hand, SCN receives the photic information from retina directly via the retinohypothalamic nerve tract (RHT). The norepinephrine engagement to beta-adrenergic receptors increases intracellular cyclic-AMP (c-AMP) which in turn activates the penultimate enzyme of melatonin biosynthesis, N-acetyltransferase (AANAT) and leads to increased melatonin synthesis and secretion at night. In the final step of melatonin biosynthesis in pineal gland, S-adenosylmethionine (SAM) is utilized by hydroxyindole-O-methyltransferase (HIOMT) as a source of methyl group and S-adenosyl-L-homocysteine (SAH) is produced. In other tissues including pineal gland, during methionine metabolism cycle, SAH is produced from SAM by a different methyl transferase, catechol-O-methyltransferase (COMT). The SAH is further hydrolysed to produce Hcy. Localization of COMT in pineal gland [285–287] provided evidence of intact methionine metabolism cycle in addition to melatonin biosynthesis. The Hcy so produced either enters into the transsulfuration pathway or remethylation pathway.