Molecular and Cellular Endocrinology 349 (2012) 13–19

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Circadian regulation of pineal gland rhythmicity

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ARTICLE INFO

Article history:
Available online 18 July 2011

Keywords:
Pineal gland
Melatonin
Circadian rhythms

ABSTRACT

The pineal gland is a neuroendocrine organ of the brain. Its main task is to synthesize and secrete melatonin, a nocturnal hormone with diverse physiological functions. This review will focus on the central and pineal mechanisms in generation of mammalian pineal rhythmicity including melatonin production. In particular, this review covers the following topics: (1) local control of serotonin and melatonin rhythms; (2) neurotransmitters involved in central control of melatonin; (3) plasticity of the neural circuit controlling melatonin production; (4) role of clock genes in melatonin formation; (5) phase control of pineal rhythmicity; (6) impact of light at night on pineal rhythms; and (7) physiological function of the pineal rhythmicity.

Contents

1. Introduction

The importance of the pineal gland in circadian physiology is evident in the more than 1000 research articles published during the past decade. It is clearly a hopeless task to cover all of these articles in a single review. Fortunately, many of the published primary research papers have already been evaluated by a number of excellent review articles, which will be cited in this manuscript wherever appropriate to eliminate redundancy. While increasing numbers of studies support the role of pineal melatonin in a wide array of functions including seasonal reproduction (Goldman, 2003; Malpaux et al., 2001; Revel et al., 2009), sleep regulation (Cajochen et al., 2003; Pandi-Perumal et al., 2007, 2005; Turek and Gillette, 2004), cancer (Bartsch and Bartsch, 2006; Blask et al., 2002; Jung and Ahmad, 2006; Reiter et al., 2007) and diabetes (Nishida, 2005; Peschke, 2008; Peschke and Muhlbauer, 2010), these topics will not be covered in this manuscript. Readers who are interested in these research areas are strongly encouraged to consult the review articles cited above for in-depth discussion. In

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doi:10.1016/j.mce.2011.07.009

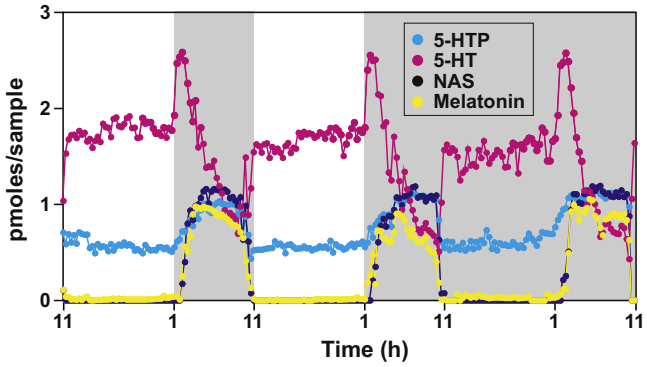

Fig. 1. Pineal gland rhythms: dietary tryptophan is sequentially converted to 5-hydroxytryptophan (5-HTP, light blue), 5-hydroxytryptamine (5-HT, pink), *N*-acetylserotonin (NAS, dark blue), and melatonin (yellow). Dark shaded areas represent dark period. Pineal rhythms over three consecutive days in one rat were monitored by pineal microdialysis.

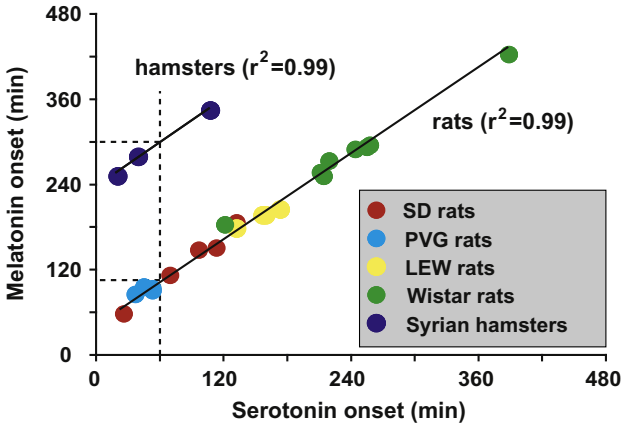

Fig. 2. Time lag between serotonin and melatonin secretion in rodents. Serotonin release precedes melatonin release by about 1 h in rat and 4 h in hamsters. In rats, the time lag is constant, regardless the strain and individual differences in timing of melatonin release.

this review, we will focus on the central and local mechanisms regulating amplitude and timing of melatonin synthesis in the mammalian pineal gland. We will discuss emerging information related to these issues and contrast published studies with those from our own laboratory, aiming to identify gaps in our knowledge on in vivo regulation of pineal rhythmicity.

The pineal gland is an unpaired neuroendocrine organ situated in the midline of the brain. Its primary function is to transduce light and dark information to whole body physiology via the release of hormone melatonin (Arendt, 2005). Melatonin is synthesized from the amino acid tryptophan via four sequential enzymatic steps (Borjigin et al., 1999): conversion of dietary amino acid tryptophan to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase 1 (TPH1); synthesis of 5-hydroxytryptamine (5-HT or serotonin) by aromatic amino acid decarboxylase; formation of *N*-acetylserotonin (NAS) by arylalkylamine *N*-acetyltransferase (AANAT), and production of melatonin by hydroxyindole-*O*-methyltransferase (HIOMT) (also termed *N*-acetylserotonin methyltransferase or ASMT). All four enzymatic derivatives of tryptophan display circadian rhythms of release in the rat pineal gland with higher levels at night (Fig. 1). Unlike NAS and melatonin that are barely detectable during the daytime, both 5-HTP and serotonin are released at relatively high levels during the day and increase further at night.

2. Local control of pineal rhythmicity

2.1. Local control – serotonin formation

The pineal gland receives adrenergic innervation, which activates a cascade of circadian events that leads to the nightly formation of melatonin from serotonin. Serotonin is present at high levels in the pineal gland during the day and increases further at night in the absence of melatonin formation (Sun et al., 2002). In the presence of melatonin synthesis, however, 5-HTP (Bach et al., 2010; Champney et al., 1984) and serotonin (Snyder and Axelrod, 1965; Snyder et al., 1965) content of the rat pineal gland is below their daytime levels due to their consumption by melatonin synthesis (Sun et al., 2002). The increased nocturnal synthesis of serotonin is driven by increased enzyme activity (Ehret et al., 1991; Shibuya et al., 1977; Sitaram and Lees, 1978) and protein levels (Huang et al., 2008) of TPH1, the rate-limiting enzyme of serotonin production. Post-translational control by phosphorylation of serine-58 stabilizes the TPH1 protein to elevate serotonin production at night (Huang et al., 2008).

Serotonin secretion displays biphasic patterns at night with an early peak in amplitude, followed by sustained decrease in concentration for the remainder of the night [Fig. 1; see (Sun et al., 2002)]. In both rats and hamsters where AANAT activation is transcriptionally controlled, serotonin release surges during early night and precedes melatonin onset [Fig. 2; (Liu and Borjigin, 2006)]. In contrast to the rat pineal gland where serotonin release surges 1 h earlier than melatonin onset, Syrian hamsters show a lag of 4 h between serotonin surge and melatonin induction [Fig. 2; (Liu and Borjigin, 2006)]. These data indicate that mechanisms of transcriptional activation of melatonin synthesis downstream of adrenergic stimulation in the pineal differ between rats and hamsters, a finding consistent with studies conducted in other laboratories (Simonneaux and Ribelayga, 2003; Simonneaux et al., 2006). In the degu pineal gland where AANAT activation is regulated post-transcriptionally, however, nocturnal surge of serotonin release was undetectable (Lee et al., 2009). These data suggest that nightly stimulation of adrenergic signaling leads to an immediate activation of TPH1 (posttranscriptional) and a delayed stimulation of AANAT (transcriptional), which generates a sequential surge of secretion of serotonin and melatonin (Huang et al., 2008; Liu and Borjigin, 2006; Sun et al., 2002). When both TPH1 and AANAT are stimulated post-transcriptionally in degus, the time lag of secretion between serotonin and melatonin disappears (Chattoraj et al., 2009; Lee et al., 2009).

2.2. Local control – melatonin formation

Melatonin production from serotonin requires activities of both AANAT and HIOMT. In humans, decreased melatonin levels are found in patients with Alzheimer's disease (Liu et al., 1999; Mishima et al., 1999), age-related macular degeneration (Rosen et al., 2009); or autism spectrum disorders (Melke et al., 2008; Nir et al., 1995; Tordjman et al., 2005). In addition, disrupted melatonin production in shift workers is considered a risk factor for increased breast cancer rates (Blask et al., 2009). It is therefore critical to define the key step of melatonin synthesis in vivo. Classically AANAT has been considered the rate-limiting enzyme of melatonin production (Klein, 2007) ever since the discovery of its striking diurnal rhythms in enzyme activity (Klein and Weller, 1970). During daytime, AANAT clearly limits the production of melatonin since its enzyme activity is low. For the bulk of night, however, AANAT does not limit the amplitudes of melatonin formation (Liu and Borjigin, 2005c). Several lines of evidence from the past few years support this view: (1) A strain of rats harboring