Role of Melatonin in Anesthesia and Intensive Care

An Essay

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Introduction

Delirium, which is also known as an acute confusional state, is a syndrome characterized by disturbance in consciousness (i.e., reduced clarity of awareness of the environment), change in cognition including alteration in attention, disorganized thinking, disturbed psychomotor activity, and abnormal sleep-wake cycle ***(Sultan, 2010).***

Melatonin, once labelled as a master hormone, is a natural substance present in all major taxa of organisms. It is produced mainly in the pineal gland of all mammals and vertebrates and its secretion is high during night time and low during day time. Melatonin is also synthesized in a number of other organs and peripheral tissues from tryptophan. Melatonin has a spectrum of important properties and plays several important physiological roles, many of which can have important clinical applications. Some experimental studies and clinical trials are providing the basis for future clinical applications of melatonin of use to the anesthesiologist ***(*Madhuri S and Tushar*, 2013).***

Intensive care delirium is a well-recognized complication in critically ill patients. Delirium is an independent risk factor for death in the intensive care unit (ICU), leading to oversedation,

increased duration of mechanical ventilation, and increased length of stay. Although there has not been a direct causal relationship shown between sleep deprivation and delirium, many studies have demonstrated that critically ill patients have an altered sleep pattern, abnormal levels of melatonin, and loss of circadian rhythms. Melatonin has a major role in control of circadian rhythm and sleep regulation and other effects on the immune system, neuroprotection, and oxidant/anti-oxidant activity. There has been interest in the use of exogenous melatonin as a measure to improve sleep ***(Bellapart and Boots, 2012).***

Exogenous melatonin has a number of beneficial actions, first and foremost is its use in the treatment of sleep disorders and jet leg. In addition to sleep promotion, melatonin exerts numerous other sedative and anti-excitatory effects that clearly go beyond sleep induction since they are also observed in nocturnally-active animals. This has been frequently studied in relation to its anticonvulsant actions, which have been linked to a facilitating role of melatonin on γ-aminobutyric acid (GABA) transmission. Experimental data support the analgesic and sedative role of melatonin. In adult human, its analgesic role has been employed for treatment of diseases with chronic pain. The hypnotic property of melatonin supports its possible use in different stages during anesthetic procedures, from premedication to induction of general

anesthesia for the modulating effects of melatonin on anesthesia drugs ***(Marseglia et al, 2015).***

Aim of work

The goal of this work is to review the physiological properties of melatonin and how these could prove useful for several clinical applications in perioperative management, critical care and pain medicine.

Chapter 1

Melatonin physiology

➢ Introduction:-

Melatonin (N-acetyl-methoxytryptamine) is a hormone produced in the brain by the pineal gland from the amino acid tryptophan ***(Sultan, 2010).*** And was isolated and characterized from the bovine pineal gland by the dermatologist **Aaron Lerner** in 1958.It`s the main hormone secreted by the pineal gland and secondary sources are retina, gut, skin, platelets and bone marrow. ***(Lerner, et al.1958)*** Melatonin is an indole compound, is synthesized from serotonin. Melatonin has been found integral to circadian rhythms and sleep regulation in addition to effects on immune function, cell growth, and other endocrine regulation. Clinically, melatonin has been studied and used for a wide variety of sleep disorders ***(Buscemi et al., 2006).***

➢ Melatonin Biosynthesis:-

Melatonin, or N-acetyl-methoxytryptamine, is synthesized within the pinealocytes from the amino acid tryptophan ***(Bellapart and Boots, 2012)*** which is taken up from the circulation and transformed into serotonin, which is then converted into melatonin by a two-step process involving the sequential activities of two enzymes, serotonin- N -

acetyltransferase (NAT) and hydroxyindole- *O* methyltransferas (HIOMT) ***(Klein and Moore, 1979). (Fig. 1)***.

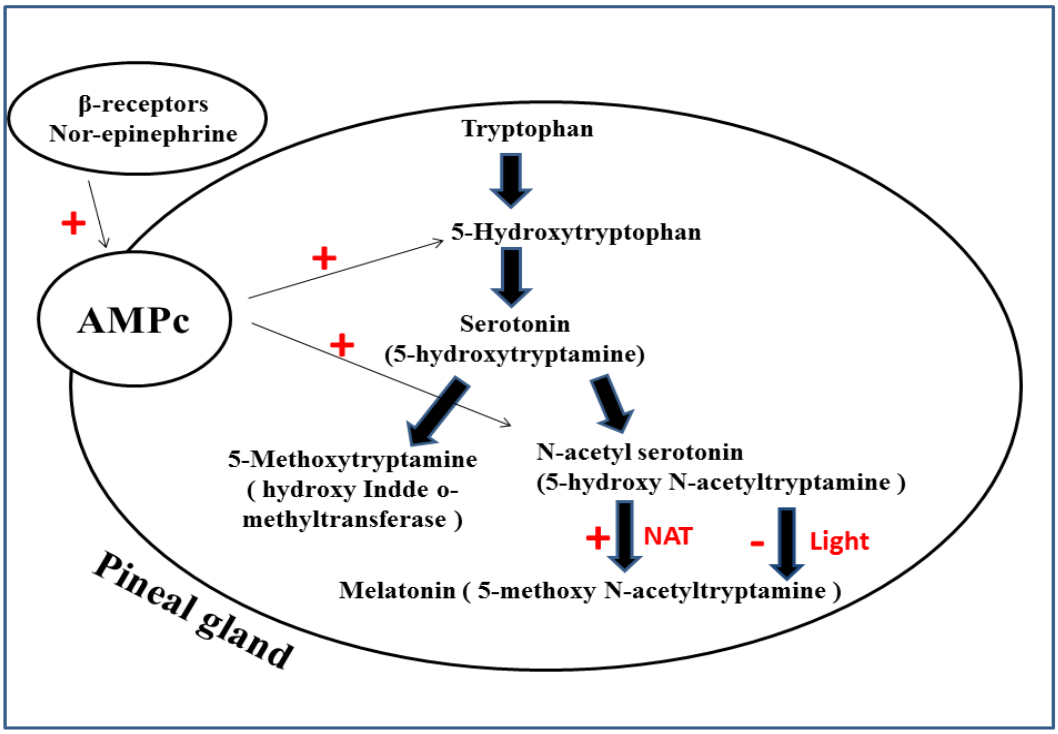

Fig. 1: Synthesis of endogenous melatonin *(Bellapart and Boots, 2012).*

Sympathetic innervation of the pineal gland (specifically via norepinephrine) is the major transmitter involved in the synthesis of melatonin. Cyclic adenosine monophosphate (AMPc) activation acts as second messenger, stimulating serotonin-N-acetyltransferase, to produce serotonin from tryptophan. While the availability of serotonin is a limiting factor in the synthesis of melatonin, serotonin-N acetyltransferase increases its activity 100-fold during darkness.

The rate-limiting enzyme is N-acetyltransferase (NAT) whose synthesis is promoted by darkness with its activity modulated by multiple neuronal interactions mainly based in the suprachiasmatic nuclei (SCN)***(Fu and Lee, 2003).***

Although the pineal gland is the main site for the synthesis of melatonin, other sites such as the testis, retina, and the gastrointestinal tract contribute, to a lesser extent, to the circulating levels of melatonin ***(Bubenik, 2001).*** Endogenous melatonin is first released around 6–8 weeks after birth with peak secretion at 3–5 yr, followed by a steady-state phase during puberty and a progressive decline through adulthood ***(Bellapart and Boots, 2012).***

Light induces NAT proteolysis, leading to a rapid decline in melatonin synthesis. Declining levels of these clock-proteins trigger gene transcription and a new cycle of melatonin synthesis with peak activation at night. The environmental cues that regulate an organism's biological clock are predominantly the daily alternation of light and darkness acting via the retina and retino-hypothalamic pathways directly on the SCN ***(Fig. 2)*** ***(Lewy, et al., 1998).***

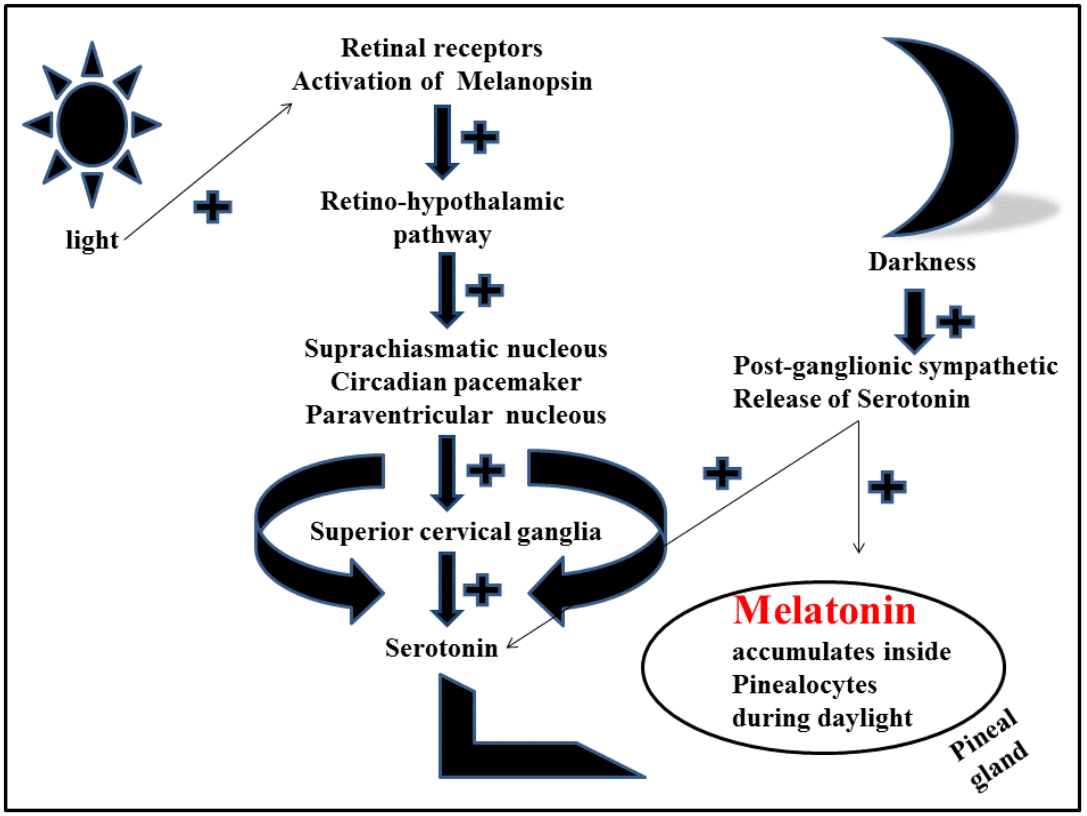

Fig 2: Physiological pathways for the synthesis of melatonin *(Lewy AJ et al., 1998).*

Direct light activates melanopsin (a photo-pigment within the retina), leading to pupillary constriction, suppression of circadian rhythms, regulation of alertness, and cognitive functions with suppression of the release of melatonin. Light inhibits the release of melatonin from the pineal gland and promotes its storage after formation during dark cycles. Darkness stimulates post-ganglionic serotonin which directly stimulates the release of melatonin from the pineal gland.

Melatonin synthesis depends upon tryptophan availability, as it is reduced after acute tryptophan depletion ***(Zimmermann, et al.1993).***Other nutritional factors might also influence melatonin synthesis, for example, folate status and levels of vitamin B6, a

coenzyme in tryptophan decarboxylation that can stimulate melatonin production in prepubertal children, but not in adults ***(Luboshitzky , et al.2002)***

➢ Melatonin Secretion:-

Melatonin displays high lipid and water solubility which facilitates its passage across cell membranes ***(Pardridge and Mietus, 1980).*** After its release into the circulation, it gains access to various fluids, tissues, and cellular compartments (saliva, urine, cerebrospinal fluid, pre-ovulatory follicle, semen, amniotic fluid, and milk). As melatonin is not stored in the pineal, its plasma profile faithfully refects pineal activity. Blood melatonin is bound mainly to albumin (70 %) ***(Reiter, 1991).***

Melatonin secretion increases directly with the length of darkness. Increased light intensity both increases the quantity of endogenous melatonin produced and shifts the pattern of release throughout the circadian clock (melatonin synchronization). In blind people, there is no synchronization of melatonin release, a state known as ‘free-running’ ***(Lewy et al., 1998).***Endogenous melatonin is released at night beginning around 21:00 with peak release between 2:00 and 4:00. Melatonin release is inhibited typically between 7:00 and 9:00, coinciding with the peak of endogenous cortisol. The average concentrations of melatonin in plasma are in the order of 60–70 $pg.ml^{-1}$, with the oscillating