


Melatonin receptors: distribution in mammalian brain and their respective putative functions

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Received: 8 December 2016 / Accepted: 28 April 2017 / Published online: 6 May 2017
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Abstract Melatonin, through its different receptors, has pleiotropic functions in mammalian brain. Melatonin is secreted mainly by the pineal gland and exerts its effects via receptor-mediated and non-receptor-mediated actions. With recent advancement in neuroanatomical mapping, we may now understand better the localizations of the two G protein-coupled melatonin receptors MT1 and MT2. The abundance of these melatonin receptors in respective brain regions suggests that receptor-mediated actions of melatonin might play crucial roles in the functions of central nervous system. Hence, this review aims to summarize the distribution of melatonin receptors in the brain and to discuss the putative functions of melatonin in the retina, cerebral cortex, reticular thalamic nucleus, habenula, hypothalamus, pituitary gland, periaqueductal gray, dorsal raphe nucleus, midbrain and cerebellum. Studies on melatonin receptors in the brain are important because cumulative evidence has pointed out that melatonin

receptors not only play important physiological roles in sleep, anxiety, pain and circadian rhythm, but might also be involved in the pathogenesis of a number of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and Huntington's disease.

Keywords Melatonin receptor · Circadian rhythm · Neurogenesis · Nociception · Depression · Neurodegenerative disease

Introduction

Melatonin (5-methoxy-*N*-acetyltryptamine) is a pleiotropic hormone that regulates a broad range of body functions. It is the main hormone synthesized and secreted by the pineal gland during the dark cycle in accordance with the 24-h sleep cycle (Pévet 2002). Once secreted, it enters into the blood circulatory system through which it travels to and acts on different regions of the body to achieve desirable physiological responses. Melatonin has high accessibility throughout the body due to its amphiphilic nature (Costa et al. 1995). The ubiquitous distribution of melatonin has allowed it to exert highly versatile functions throughout the body. The response is often mediated through specific melatonin receptors in the target cells. On top of that, melatonin also acts as an antioxidant and free radical scavenger without the involvement of its receptors (Reiter et al. 2007; Pechanova et al. 2014; Galano et al. 2013). A detailed review regarding the actions of melatonin in the periphery has been published recently (Slominski et al. 2012).

In the brain, melatonin penetrates the blood–brain barrier easily, which allows it to exert its effects onto different brain

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regions (Gilgun-Sherki et al. 2001). Presence of melatonin receptors in the brain, as demonstrated by a few published studies (Lacoste et al. 2015; Mazzucchelli et al. 1996; Adamah-Biassi et al. 2014), has provided evidence of involvement of melatonin in brain functions. Of recent note is the study by Lacoste et al. (2015), which reported the first neuroanatomical mapping of the distribution of melatonin receptor proteins in the rat brain. To date, a full mapping of the melatonin receptors in human brain has yet been studied. There is also a lack of comprehensive review that elaborates the role and the functions of melatonin receptors in various brain regions. Understanding the actions of melatonin in the brain is important as experimental evidence has implicated the involvement of melatonin in multiple physiological functions in the brain. This review attempts to compile the identified localizations of melatonin receptors and summarize the putative functions of melatonin in the mammalian brain. Only brain regions that have suggestive roles of melatonin supported by other studies (except pineal gland) are selected to be included in this review.

Melatonin receptors

Melatonin receptors are members of the seven transmembrane G protein-coupled receptors (GPCRs) superfamily (Witt-Enderby et al. 2003). Currently, three subtypes of melatonin receptors have been identified in mammals: MT1 (formerly Mel 1a or ML_{1A}), MT2 (formerly Mel 1b or ML_{1B}), and MT3 (formerly ML₂) (Dubocovich et al. 2010). MT1 and MT2 remain to be the main GPCRs identified in the mammalian brain. In mammals, MT3 is identified as a melatonin-binding site located on a cytosolic enzyme, quinone reductase 2 (Nosjean et al. 2000). It generally has low binding affinity with melatonin (Luchetti et al. 2010).

MT1 receptor

The Mel1c receptor in frogs (*Xenopus laevis*) was the first melatonin receptor to be cloned (Ebisawa et al. 1994). Its discovery was vital in facilitating the cloning of other mammalian melatonin receptors, as the same group who cloned the Mel1c receptor was also the first to clone the MT1 receptor from the sheep and human (Reppert et al. 1994). MT1 receptor is 350 amino acids long with a molecular weight of 39,374 Da (Song et al. 1997). It is characterized as a receptor linked to a pertussis toxin-sensitive guanine nucleotide-binding protein (G protein) that mediates inhibition of adenylyl cyclase in native tissues (Carlson et al. 1989). Through the use of 2-[125I]Iodomelatonin, the MT1 receptor has been found to be expressed in various brain regions such as the pars tuberalis, hypothalamus, and peripheral tissues including the cardiovascular system,

gastrointestinal tract, immune system and the kidney in mammals (Dardente et al. 2003; Wu et al. 2013; Slominski et al. 2012; Bubenik 2002; Song et al. 1992).

MT2 receptor

The expression of MT2 receptor was reported in multiple organs including the retina, brain, and the gastrointestinal tract (Wiechmann and Sherry 2013; Morgan et al. 1994; Bubenik 2002). The MT2 receptor was cloned just one year after the MT1 receptor was cloned (Reppert et al. 1995). The MT2 receptor is 362 amino acids long with a molecular weight of 40,188 Da and it shares 60% homology to the MT1 receptor (Reppert et al. 1996). Both melatonin receptors are classified under the same GPCR class and in this class, sequence homology between receptors mostly occurs within the transmembrane domains (Deupi et al. 2007; Dubocovich et al. 2010). Similarly, the MT2 receptor is also linked to G protein-coupled receptors and is involved in the inhibition of adenylyl cyclase and soluble guanylyl cyclase pathways (Petit et al. 1999).

Cellular signaling mechanism of melatonin receptors

The cellular signaling pathways for melatonin receptors vary in different species (Hardeland 2009). However, a few principal signaling pathways exist to be commonly activated upon melatonin stimulation. Both MT1 and MT2 receptors are closely linked to the pertussis toxin-sensitive G_i protein and activation of this protein inhibits the AC/cAMP/PKA/CREB pathway (Rivera-Bermudez et al. 2004; Tosini et al. 2014). Through the MT2 receptor, inhibition of the GC/cGMP/PKG pathway can also occur upon G_i activation (Petit et al. 1999). In addition, the activation of the phospholipase C pathway that leads to increase in inositol triphosphate (IP₃) and 1, 2-diacylglycerol (DAG) levels has been demonstrated for both MT1 and MT2 receptors (Sharkey and Olcese 2007; Witt-Enderby et al. 2003). This activation is found to be linked to pertussis toxin-insensitive G_q protein and the MT1/MT2 heterodimer shows an augmented activation for these pathways, indicating that there are positive allosteric interactions between the two receptors (Jockers et al. 2008).

Distribution of melatonin receptors in the mammalian brain

In the past, the identification of melatonin receptors in the mammalian brain was largely performed through indirect means using non-selective radioligand 2-[125I]Iodomelatonin

to identify high-affinity melatonin-binding sites in autoradiography (Weaver et al. 1993; Al-Ghoul et al. 1998; Stankov et al. 1992; Dubocovich et al. 1996; Masson-Pevet et al. 1994; Williams 1989; Williams et al. 1997; Siuciak et al. 1990). Recently, immunoreactive approach complemented with PCR analysis and in situ hybridisation has become the more popular method for the same investigation (Adi et al. 2010; Wu et al. 2006; Klosen et al. 2002; Lopez-Canul et al. 2015b; Lacoste et al. 2015; Mazzucchelli et al. 1996; Uz et al. 2005; Musshoff et al. 2002; Savaskan et al. 2002a, 2005; Brunner et al. 2006; Hunt et al. 2001; Sugden et al. 1999; Waly and Hallworth 2015; Uz et al. 2003; Poirel et al. 2002; Neu and Niles 1997). Recently a transgenic animal model which uses MT1 promoter to drive the expression of red fluorescence protein has also been developed to study the distribution of melatonin receptors (Adamah-Biassi et al. 2014).

Each of these methods has its own limitations. For instance, the autoradiographical approach is unable to discriminate the type of melatonin receptors involved. Also the binding affinity can be significantly reduced by the dimerization of melatonin receptors with their family members or other G protein-coupled receptors (Adamah-Biassi et al. 2014). Meanwhile, the transgenic animal model has unexpectedly failed to locate the MT1 receptors in the

suprachiasmatic nucleus (SCN) or the striatum. The presence of MT1 receptor in SCN (Waly and Hallworth 2015) and striatum (Uz et al. 2003) of rodents has been confirmed previously in other studies. Authors have attributed this observation to the incomplete inclusion of regulatory elements crucial for the MT1 expression and also the possible integration of transgene in the chromosomal location where the gene expression is repressed in these brain regions (Adamah-Biassi et al. 2014). Nevertheless, the biggest challenge in the melatonin receptor research is the lack of reliable antibodies which would allow specific binding to the melatonin receptors with high sensitivity. In fact, many groups have resorted to complement immunoreactive approach with the results derived from PCR and in situ hybridisation to obtain a more complete set of data.

Nevertheless, as the autoradiographical approach is unable to discriminate the type of melatonin receptors involved we have listed mainly the studies that have used the immunoreactive, PCR analysis, in situ hybridisation and transgenic animal models to report the presence of melatonin receptors. The types of melatonin receptors in different brain regions and the source references are summarized in Table 1. The detailed distribution of MT1 and MT2 receptors based on these studies are summarized in Table 2.

Table 1 Types of melatonin receptors in mammalian brain

| Brain regions | Type of melatonin receptor | Origin and references |
|----------------------------|----------------------------|---|
| Retina | MT1, MT2 | Rat (Fujieda et al. 1999; Sallinen et al. 2005; Yang et al. 2011) Guinea pig (Fujieda et al. 2000) Human (Meyer et al. 2002; Reppert et al. 1995; Savaskan et al. 2002b, 2007; Scher et al. 2002) |
| Cerebral cortex | MT1, MT2 | Mouse (Adamah-Biassi et al. 2014) Rat (Lacoste et al. 2015; Musshoff et al. 2002) Human (Mazzucchelli et al. 1996; Uz et al. 2005; Savaskan et al. 2002a, 2005) |
| Reticular thalamic nucleus | MT2 | Rat (Lacoste et al. 2015) |
| Habenula | MT1 | Mouse (Adamah-Biassi et al. 2014) Rat (Lacoste et al. 2015) |
| Hypothalamus | MT1, MT2 | Rat (Hunt et al. 2001; Lacoste et al. 2015; Neu and Niles 1997; Poirel et al. 2002; Sallinen et al. 2005; Sugden et al. 1999; Waly and Hallworth 2015) Human (Weaver and Reppert 1996; Weaver et al. 1993; Wu et al. 2006, 2013) |
| Pituitary gland | MT1 | Rat (Lacoste et al. 2015; Klosen et al. 2002) Human (Weaver et al. 1993; Wu et al. 2006) |
| Periaqueductal gray | MT1, MT2 | Mouse (Adamah-Biassi et al. 2014) Rat (Lacoste et al. 2015; Lopez-Canul et al. 2015b) |
| Dorsal raphe nucleus | MT1 | Rat (Lacoste et al. 2015) |
| Midbrain | MT1, MT2 | Rat (Lacoste et al. 2015) Human (Uz et al. 2005; Adi et al. 2010; Uz et al. 2003) |
| Cerebellum | MT1, MT2 | Mouse (Adamah-Biassi et al. 2014) Rat (Lacoste et al. 2015) Human (Mazzucchelli et al. 1996; Al-Ghoul et al. 1998) |

Table 2 Distribution of melatonin receptors in the brain Table modified with permission from Lacoste et al. (2015)

| Brain regions | MT1 immunoreactivity | MT2 immunoreactivity |
|----------------------------------|----------------------|----------------------|
| Cerebral cortex | | |
| Prefrontal | + | 0 to + |
| Retrosplenial | +++ | + |
| Occipital | + | – |
| Basal forebrain | | |
| Islands of Calleja | +++ | + |
| Medial forebrain bundle | ++ | ++ |
| Ventral pallidum | ++ | ++ |
| Hippocampus | | |
| CA1 | + | + |
| CA2 | + | + to ++ |
| CA3 | + to ++ | +++ |
| Dentate gyrus | + | ++ |
| Basal ganglia | | |
| Nucleus accumbens | 0 to + | – |
| Caudate–putamen | – | – |
| Globus pallidus | + | + to ++ |
| Epithalamus | | |
| Lateral habenula | + | – |
| Medial habenula | +++ | – |
| Thalamus | | |
| Anterodorsal nucleus | ++ | – |
| Reticular nucleus | – | +++ |
| Ventromedial nucleus | + | ++ |
| Hypothalamus | | |
| Paraventricular nucleus | – | + |
| Supraoptic nucleus | – | +++ |
| Medial eminence | + | ++ |
| Suprachiasmatic nucleus | ++ to +++ | – |
| Dorsal mesencephalon | | |
| Superior colliculi | +++ | + |
| Inferior colliculi | ++ to +++ | ++ to +++ |
| PAG | | |
| Ventrolateral PAG | + | ++ |
| Dorsal raphe nucleus | ++ | + |
| Ventral mesencephalon | | |
| Substantia nigra pars compacta | ++ to +++ | |
| Substantia nigra pars reticulata | ++ to +++ | |
| Pituitary gland | | |
| Pars tuberalis | +++ | – |
| Cerebellum | | |
| Molecular layer | + | + |
| Granular layer | 0 to + | 0 to + |

Putative functions of melatonin

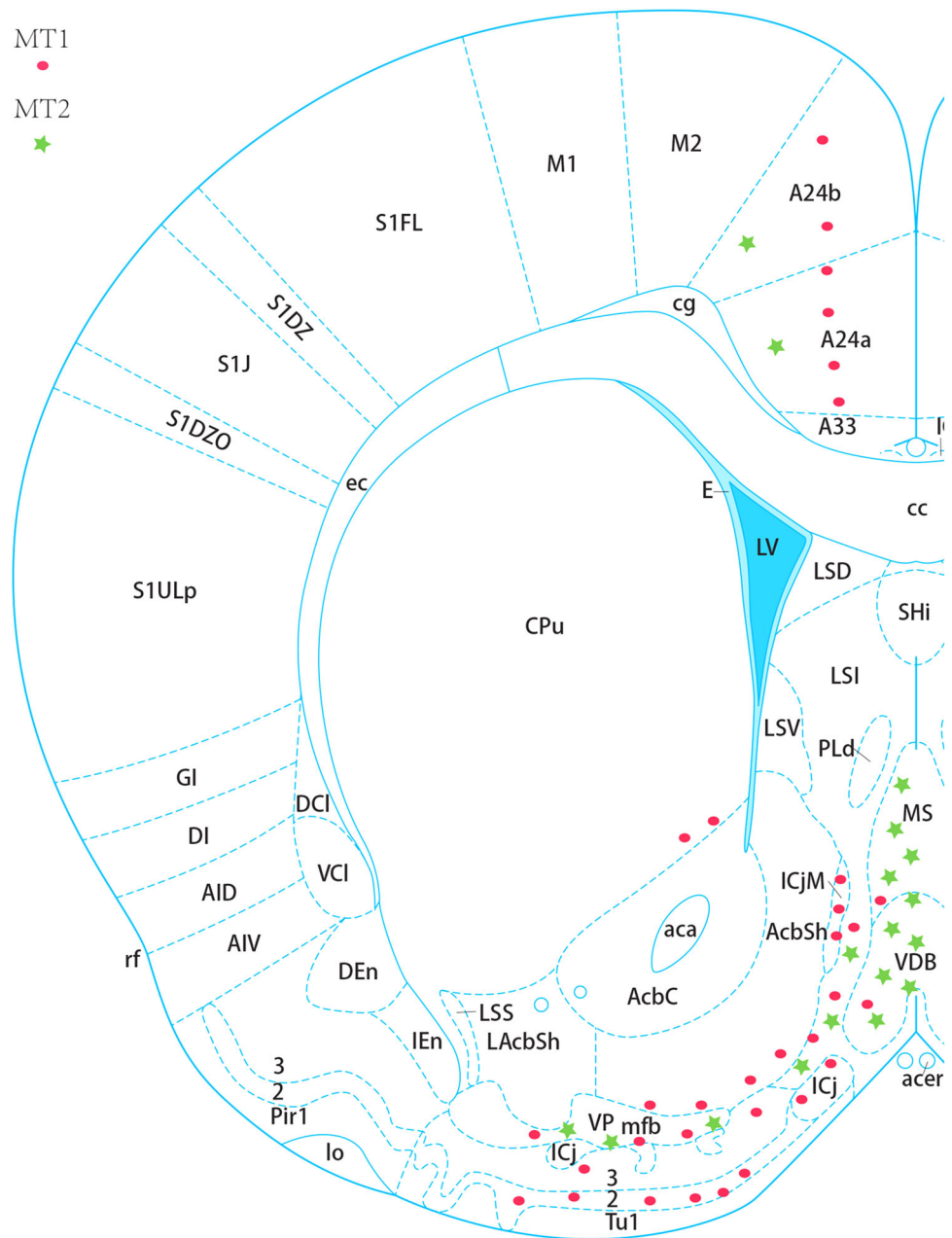
In this section, brain regions that express melatonin receptors and have existing evidence suggestive of melatonin involvement in the functionality are selected. These include retina, cerebral cortex, reticular thalamic nucleus, habenula, hypothalamus, pituitary gland, periaqueductal gray, dorsal raphe nucleus, midbrain and cerebellum. The schematic drawings mapped the majority of nuclei which had either MT1/MT2 receptor or both receptor-positive neurons on the plates from the rat atlas (modified with permission from Paxinos and Watson 2013) (Figs. 1, 2, 3, 4). The areas where receptors have been located for both MT1 and MT2 receptors are summarized in Table 2 (modified with permission from Lacoste et al. 2015). Putative functions of these regions are compiled in Table 3.

Retina

The synchronization of the circadian clock to the 24-h light/dark cycle is achieved through both external and internal stimuli. Light and dark signals received by the retina act as the external stimulus to the SCN and in turn, the SCN controls circadian regulation of melatonin synthesis in the retina (Wiechmann and Sherry 2013). In mammals, RT-PCR and immunohistochemistry studies have shown that MT1 mRNA and protein are localized to the inner and outer plexiform layers (IPL and OPL), inner nuclear layer, ganglion, amacrine, horizontal cells, and rod and cone photoreceptor cells (Scher et al. 2002; Fujieda et al. 1999, 2000; Sallinen et al. 2005). MT2 receptor immunoreactivity was localized to the ganglion and bipolar cells in the inner nuclear layer of the retina, the inner segments of the photoreceptor cells and cellular processes in IPL and OPL of the retina (Savaskan et al. 2007; Sallinen et al. 2005; Yang et al. 2011; Reppert et al. 1995).

Retinal melatonin is synthesized and secreted by photoreceptors and acts as a paracrine hormone, having a localized action upon the retina. It modulates light sensitivity and neurotransmitter release, which are some of the actions retinal melatonin is involved in (Wiechmann and Sherry 2013). Regulation of neurotransmitter release appears to be mediated by MT1 receptors on amacrine cells. As melatonin is secreted from photoreceptors, it binds to melatonin receptors on specific amacrine cells and subsequent release of dopamine and GABA is regulated (Fujieda et al. 2000). Dopamine and melatonin are mutually antagonistic hormones. Binding of melatonin to receptors on dopaminergic amacrine cells inhibits the release of dopamine while dopamine binding to D2 dopamine receptors suppresses melatonin synthesis. Circadian

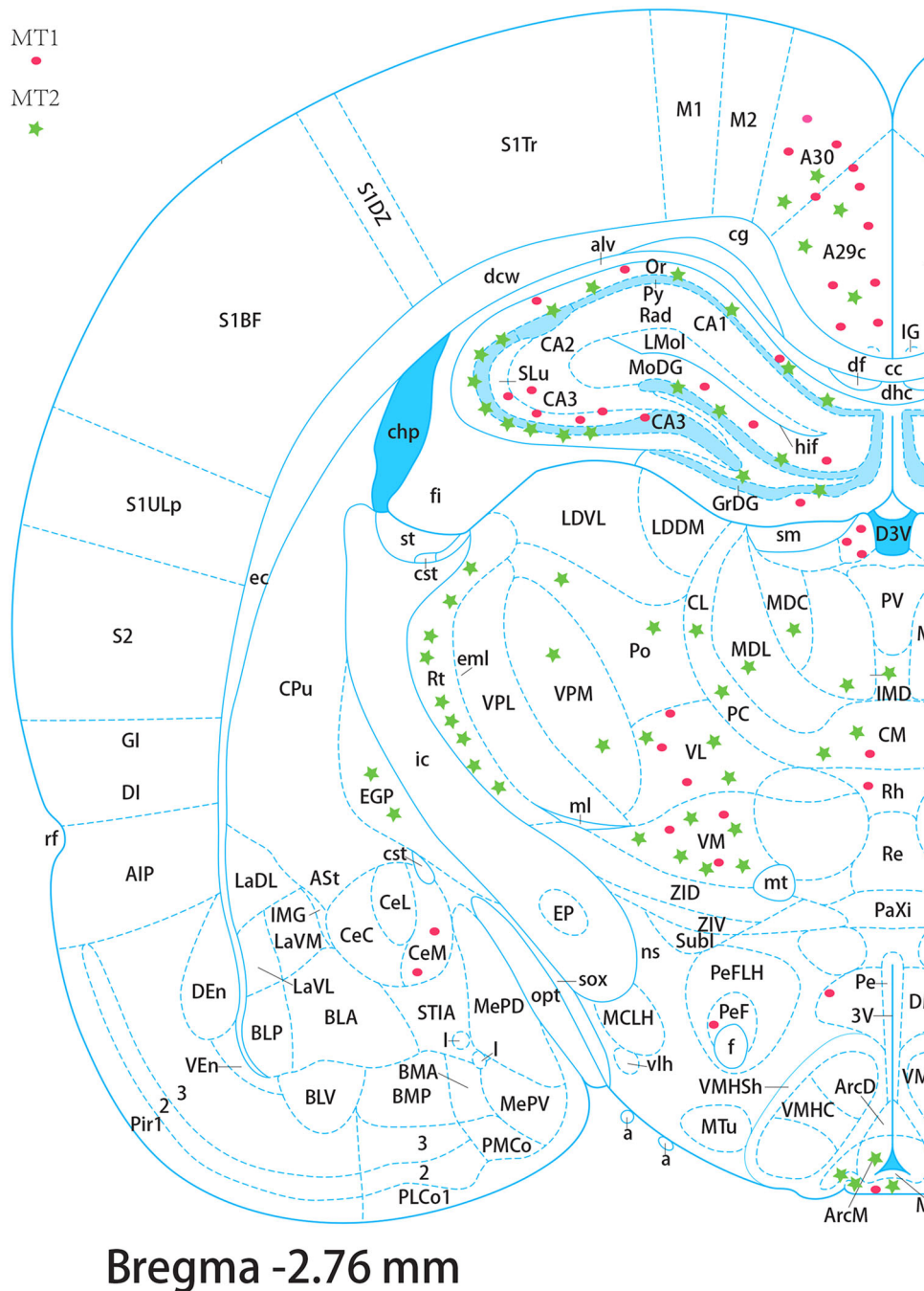
Fig. 1 Distribution of MT1 and MT2 receptor in the rostral forebrain. MT1 receptor immunoreactivity is weak to moderate in the cingulate cortex (A24a and A24b), and mainly in layers II/III. MT2 receptor immunoreactivity is sparse in layer V in the cingulate cortex. MT1 receptor immunoreactivity is strong in the islands of Calleja (ICj) in contrast to the weak MT2 receptor immunoreactivity. Both MT1 and MT2 receptor immunoreactivity is moderate in the ventral pallidum (VP). Only MT1 receptor immunoreactivity is present in the shell region of the nucleus accumbens (AcbSh). Medially, in the rostral septum, only weak MT1 receptor immunoreactivity is present in the septum and the nucleus of the vertical limb of the diagonal band (VDB), in contrast to the moderate immunoreactivity of MT2 receptor



Bregma 1.28 mm

release of melatonin results in opposing levels of melatonin and dopamine and this regulates light sensitivity of the retina (Megaw et al. 2006). For example, melatonin, synthesized at night, could increase visual sensitivity through binding to MT1 receptors. Binding of melatonin to MT1 receptors results in inhibition of dopamine release which would facilitate dark adaptation through the increase of horizontal cell coupling (Harsanyi and Mangel 1992). Therefore, it is possible that MT1 and/or MT2 melatonin receptors in amacrine and/or ganglion retinal cells

modulate the retino-hypothalamic transmission of the light–dark signal via regulation of dopaminergic and GABAergic transmission (Dubocovich and Markowska 2005). Also, two studies from the same group have reported decreased immunoreactivities of MT1 and MT2 receptors in the retina of Alzheimer’s disease (AD) patients (Savaskan et al. 2002b, 2007). Nevertheless, the involvement of melatonin receptors in the pathophysiology of AD is unclear and requires further confirmation by future studies.



Melatonin and its receptors have been shown to modulate visual function and clearly demonstrated that they are indeed key players in retinal physiology. The actions of melatonin on retina seem to be primarily mediated through the regulation of selected neurotransmitters. However, the multiple targets of melatonin in the retina, such as photoreceptors and ganglion, lead to complex actions and the specific functions of each melatonin receptor subtypes in different sections of the retina remain to be investigated.

Cerebral cortex

A few studies have reported the distribution of melatonin receptors in the cerebral cortex. Lacoste et al. (2015) found that the cerebral cortex is rich in MT1 receptor, but not MT2 receptor. The majority of MT1 receptor-positive neurons were found in layers II/III and V, whereas MT2 receptor-positive neurons were mainly in deeper layers (V and VI) of cortical areas. The density of MT1 receptor-positive neurons was highest in the retrosplenial cortex and

Fig. 2 Distribution of MT1 and MT2 receptor in the middle forebrain. MT1 receptor immunoreactivity is moderate to strong in the cingulate cortex (A29 and A30), and mainly in layers II/III. MT2 receptor immunoreactivity is sparse in layer V in the cingulate cortex. In the rostral hippocampus, few MT1-positive neurons are present in the CA1 region, and weak labeling in the CA2 region, whereas weak to moderate labeling in the CA3 region. MT2 receptor immunoreactivity is moderate in the CA1 region, weak in the CA2 region, and strong in the CA3 region. MT2-positive neurons are concentrated in the pyramidal layer. In the dentate gyrus (DG), MT1 immunoreactivity is sparse and positive neurons are present mainly in the polymorph layer (PoDG). MT2 receptor immunoreactivity is moderate in the dentate gyrus and positive neurons are present mainly in the dorsal portion of the granular layer (GrDG). In the rostral thalamus, MT1 receptor immunoreactivity is almost exclusively associated with dendritic processes in the thalamus except few neurons in the central medial (CM) and the rhomboid thalamic (Rh) nuclei, whereas MT2 receptor immunoreactivity is weak in the mediodorsal (MD), central medial (CM), and ventrolateral nuclei (VL), and moderate in the reticular nucleus (Rt). In the middle and posterior third of the thalamus, MT2 receptor immunoreactivity is weak in the centrolateral (CL), mediodorsal (MD), ventral posterolateral (VPL) and posterior (Po) thalamic nuclei, moderate in the caudal part of the ventrolateral thalamic nucleus (VL), strong in the reticular (Rt) and ventromedial (VM) thalamic nuclei. In the hypothalamus, MT1 receptor immunoreactivity is weak in the dorsomedial hypothalamic (DM) and perifornical (PeF) nuclei, whereas MT2 receptor immunoreactivity is moderate in the ventral part of the arcuate (Arc) hypothalamic nucleus and the medial eminence (ME). In the medial division of central amygdaloid nucleus (CeM), MT1 receptor immunoreactivity is weak to moderate. In the globus pallidus (GP), MT2 receptor immunoreactivity is weak to moderate

decreases rostrally and caudally immediately off the midline of the brain. MT2 receptor immunoreactivity was weak in these areas and barely detectable in the medial prefrontal cortex. The immunoreactivity of MT1 receptor was weak to moderate in the more lateral areas, which was similar to that of MT2 receptor-positive neurons. MT2 receptor-positive neurons were absent in both the entorhinal and piriform cortices, and MT1 receptor-positive neurons were barely seen in these regions. In the claustrum and the endopiriform nucleus, the immunoreactivity of MT1 and MT2 receptors was weak. In the occipital (visual) and temporal (auditory) cortices, only weak signals of MT1-positive neurons were observed.

The physiological role of melatonin receptors in the cerebral cortex remains elusive. There is some evidence of involvement in cognitive function. For instance, genetic deletion of MT1/MT2 receptors seems to enhance murine cognitive performance, although the underlying mechanism is unclear (O'Neal-Moffitt et al. 2014). Besides that, it is also speculated that melatonin might act in concert with gamma-aminobutyric acid (GABA) receptors in the cerebral cortex. In a study conducted on rabbits, it was identified that the cortex contained abundant melatonin-binding sites, particularly in the parietal cortex (Stankov et al. 1992). Furthermore, binding of melatonin or 2-[125I]iodomelatonin induces benzodiazepine-like and

GABA-like effects by slowing neuronal firing. This action is likely to be mediated via melatonin receptors as the study showed that the receptor binding is sensitive to pertussis toxin, indicating that G protein-coupled receptors, such as melatonin receptors, are involved. This suggests that melatonin could possibly modulate the activity of GABA benzodiazepine receptors in the cerebral cortex (Marangos et al. 1981). This is supported by another study which demonstrated that subcutaneous injection of melatonin reversed the decrease in GABA benzodiazepine receptor density in the cerebral cortex of pinealectomized rats (Lowenstein et al. 1985). Apart from the pineal gland, astrocytes are possibly another source of melatonin in the cortex. This is supported by the presence of melatonin as well as the two key enzymes in melatonin synthesis—*N*-acetyltransferase and hydroxyindole-*O*-methyltransferase, in the rat cortical astrocytes and the glioma C6 cell line (Liu et al. 2007). Hence, it is possible that melatonin in the cortex is originated from the astrocytes.

Through the use of autoradiography, RT-PCR, immunohistochemistry and transgenic models, MT1 and MT2 receptor mRNAs and proteins have been found in the pyramidal and granular neurons in the hippocampus (Mazzucchelli et al. 1996; Savaskan et al. 2005; Adamah-Biassi et al. 2014). Distribution of MT1 receptor immunoreactivity was diffuse in the hippocampus, whereas MT2 receptor immunoreactivity is more distinct, especially in the CA3 region. In the CA1, MT1 receptor immunoreactivity was diffuse and few positive neurons were found in the pyramidal layer. In the most rostral part, diffuse immunoreactivity was found in the stratum oriens (Or) and radiatum (Rad). Weak MT1 immunoreactivity was observed in the CA2 region and weak to moderate in the CA3 region. In the dentate gyrus (DG), MT1 immunoreactivity was found in the hilus of the DG, scattered in the polymorph layer (PoDG), and absent in the granular layer. MT2 immunoreactivity was observed in all layers of the hippocampus, with moderate immunoreactivity in the CA1, weak in the CA2, and strong immunoreactivity in the CA3 region. Most of the MT2-positive neurons were found in the pyramidal layer. In the DG, MT2 immunoreactivity was moderate, with positive cell bodies in the hilus, the dorsal portion of the granular layer of DG (GrDG), and to a lesser extent in the polymorph layer of DG (PoDG) (Lacoste et al. 2015). This suggests a possible difference in the actions of the two receptors within the hippocampus.

Although the exact roles of melatonin receptors in the hippocampus are unclear, there is at least some evidence showing that chronic melatonin enhances hippocampal neurogenesis (Liu et al. 2013; Ramirez-Rodriguez et al. 2009, 2011). Studies on animal models of mental disorders/impaired brain functions have demonstrated beneficial effects of melatonin in attenuating inhibition of

Table 3 Putative functions of melatonin in different mammalian brain regions

| Brain region | Putative functions of melatonin |
|----------------------------|---|
| Retina | Regulates dopaminergic and GABAergic transmission in retino-hypothalamic transmission of the light–dark signal; possible relation to the pathophysiology of AD |
| Cerebral cortex | Improve hippocampal neurogenesis; modulation of GABAergic neurons; neuroprotection via upregulation of antioxidant enzyme expressions; reduces formation of amyloid beta peptides; memory maintenance via inhibition of LTP by MT2 receptor; possible relation to the pathophysiology of AD |
| Reticular thalamic nucleus | NREM sleep regulation by MT2 receptor |
| Habenula | Modulation of pain, depression and addiction behaviour |
| Hypothalamus | Regulates circadian rhythms and sleep/wake cycle in SCN; REM sleep regulation by MT1 receptor; temperature regulation; possible relation to the pathophysiology of PD |
| Pituitary gland | Regulation of the secretion of prolactin, vasopressin, oxytocin, corticotropin-releasing hormone and GnRH |
| Periaqueductal gray | Antinociceptive action |
| Dorsal raphe nucleus | Possible relation to pathogenesis of melancholic depression |
| Midbrain | Modulation of nigrostriatal dopaminergic pathways; modulation of mesocorticolimbic dopaminergic pathways; neuroprotection in HD by MT1 receptor; possible relation to the pathophysiology of PD and HD |
| Cerebellum | Regulation in cerebellar sensory integration; regulation of antioxidant enzymes |

Much interest gathered on the cerebral cortex and hippocampus is due to their close link with AD as susceptible brain regions. AD is an age-related, neurodegenerative disorder characterized by memory loss and cognitive deterioration. It has been reported that AD patients have reduced melatonin level in the cerebrospinal fluid (Liu et al. 1999). It was proposed at time that it was possibly a consequence of aging and neurodegeneration in AD. Later, it was identified that brain tissues from AD subjects had reduced levels of melatonin MT1 and MT2 receptors in pinealocytes and the occipital cortex compared with elderly controls (Brunner et al. 2006). Immunohistochemistry of the hippocampal regions of AD patients showed that there was a distinct decrease in MT2 receptor immunoreactivity (Savaskan et al. 2005). These results suggest the involvement of the MT2 receptor in the progression of AD although it is unknown if the loss of receptors is the consequence or the cause of AD. In contrast, the MT1 receptor immunoreactivity was found to be increased in AD (Savaskan et al. 2002a). In other regions of the brain, the MT1 receptor has been tied to melatonin's neuroprotection abilities. Therefore, it was postulated that the increase in the MT1 receptor was a compensatory mechanism responding to neuronal damage in AD to amplify neuroprotective actions of melatonin. Interestingly, prophylactic melatonin tends to reduce amyloid peptide deposition in the hippocampus although this action of melatonin is thought to be receptor independent (O'Neal-Moffitt et al. 2015). Although current evidence has demonstrated a few AD-associated changes in the pineal gland, hippocampus and the cerebral cortex, the connection between AD and melatonin receptors is still questionable.

Overall, melatonin is reported to confer neuroprotection to the cerebral cortex. Melatonin treatment protects against the ischemic stroke-induced neuronal death of the hippocampal CA1 region of the Mongolian gerbil, and this is associated with increased MT2 immunoreactivity and protein level (Lee et al. 2010). In primarily cultured rat cortical neurons, melatonin alleviated the damage from *N*-methyl-D-aspartate excitotoxicity or hypoxia/reperfusion. However, it has been pointed out that this action was likely to be a non-receptor-mediated action as it was not blunted by the melatonin antagonist luzindole (Cazevieuille et al. 1997). Nevertheless, there is evidence that melatonin upregulates the antioxidant enzymes in the cerebral cortex (Esparza et al. 2005; Kotler et al. 1998; Barlow-Walden et al. 1995). Results from the rat by Barlow-Walden et al. (1995) and Kotler et al. (1998) are generally in agreement with each other. They reported that melatonin increased mRNA levels of the glutathione peroxidase, copper–zinc-containing superoxide dismutase (Cu–Zn-SOD) and the manganese-containing superoxide dismutase (Mn-SOD) in the cortex of healthy rats. On the other hand, Esparza et al. (2005) have tested the effects of melatonin on aluminum-treated rats as an AD model. They observed that melatonin significantly increased activities of antioxidant enzymes including superoxide dismutase, glutathione peroxidase, and catalase in the cortices of aluminum-treated rats compared with those of the control rats. This study also confirmed that melatonin treatment alone would upregulate the expression of superoxide dismutase as well as catalase. In hippocampal slice cultures deprived of oxygen and glucose, melatonin reduces reactive oxygen species to near base levels. As this effect can be blocked by luzindole, it is thought that this action involves modulation of antioxidant

genes probably through receptor-mediated transcriptional signaling (Parada et al. 2014). Interestingly, dietary supplements of melatonin resulted in significant reduction in both short and long pathogenic forms of cortical amyloid beta peptides in mice (Lahiri et al. 2004). Addition of melatonin in diet seems to increase brain melatonin levels regardless of age. However, melatonin probably does not confer any memory enhancement effect as no changes in neuronal synaptic proteins were detected in mice. Similarly, another study investigated the effects of prophylactic melatonin on a transgenic AD mouse model (O’Neal-Moffitt et al. 2015). They reported that melatonin reduced amyloid beta deposition in the frontal cortex and the hippocampus, which was receptor independent. In contrast to previous reports, they also observed that melatonin reduced gene expression of antioxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase in the frontal cortex in a receptor-dependent manner. They have reasoned that this outcome was probably due to reduced oxidative stress upon long-term treatment with melatonin; hence, the need of antioxidant enzymes has reduced as well. Nevertheless, many of the above studies have the same limitation in not using melatonin agonists or KO animals to confirm the effects of receptor-mediated actions, thus it is premature to conclude that melatonin receptors confer neuroprotective effects.

Reticular thalamic nucleus

MT2 receptor, but not MT1 receptor, is found abundant in the reticular thalamic nucleus (Lacoste et al. 2015). A recent study has also shown the involvement of melatonin receptors in the reticular thalamic nucleus on sleep regulation, where spindle formation during transition to deeper sleep stages is found to be promoted by MT2 receptor agonist (Ochoa-Sanchez et al. 2011). These findings suggest a possible distinct involvement of melatonin receptors in sleep phases. MT2 receptor is involved in the NREM sleep through modulating the reticular thalamic nucleus and other areas involved in NREM, whereas MT1 receptor is involved in REM sleep through acting on brain areas such as the hypothalamus. However, more studies are still needed to understand the role played by MT1 and MT2 in different regions involved in sleep regulation and homeostasis.

Habenula

Habenula is a brain microstructure that has been thought to play roles in major depression, addiction, schizophrenia and pain processing (Boulos et al. 2016). Habenula expresses high level of MT1 receptor but not MT2 receptor (Lacoste et al. 2015; Adamah-Biassi et al. 2014).

Habenular commissure and medial habenula are the areas particularly rich in MT1 receptor. There is emerging evidence that medial habenula involves not only in pain processing (Shelton et al. 2012), but also in depression (Ranft et al. 2010) and addiction (Ranft et al. 2010). High levels of MT1 receptor in the medial habenula might implicate the involvement of MT1 receptor in these processes. As a matter of fact, MT1 receptor KO mice has demonstrated depressive behaviour and interruption in sensorimotor gating in the prepulse inhibition test, which suggests a role of MT1 receptor in depression (Weil et al. 2006; Comai et al. 2015). A recent animal study has also shown that the activation of presynaptic melatonin receptors increases the strength of glutamatergic synapses within the habenula (Evely et al. 2016). This has provided us some insight into the mechanism of how melatonin controls the function of habenula neurons.

Hypothalamus

The area of note within the hypothalamus with regards to melatonin receptor distribution is the SCN. In human, MT1 receptor protein content within the SCN is the highest. In rat, it is mainly localized on the dendrites and somas of SCN neurons (Waly and Hallworth 2015). For the MT2 receptor, its level in SCN is comparatively low. Most of it was identified in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) instead (Wu et al. 2013).

SCN is the main circadian clock in mammals and it regulates various circadian rhythms in the body when an external stimulus is received. These rhythms include diverse physiological, metabolic and behavioral ones such as the sleep cycle and levels of different hormones in mammals (Herbert 1994). One of the best known rhythms controlled by the SCN is the synthesis and secretion of melatonin from the pineal gland. The light–dark cycle of the environment acts as an external stimulus that entrains the SCN to trigger the synthesis and secretion of melatonin (Liu et al. 1997). However, melatonin holds another role in the system as endogenous melatonin is further involved in the regulation of the circadian rhythms through feedback to the SCN (Pévet 2002). In this case, melatonin may act as an internal stimulus in the circadian timing system. Furthermore, melatonin has an important action in the circadian thermoregulatory adjustment of body temperature by sending signals to the preoptic area of the anterior hypothalamus (Saarela and Reiter 1994). In short, the synthesis and secretion of melatonin is regulated by the SCN and in turn, melatonin is also able to regulate the circadian clock in set phases.

The action of melatonin upon SCN is linked to the circadian system. In fact, a recent study shows that the expression level of melatonin receptor mRNAs changes

diurnally in accordance with the melatonin release cycle. Expression of MT1 receptor mRNA reaches the peak at dusk compared to at dawn and midnight (Waly and Hallworth 2015). This result indicates that melatonin receptors are synthesized during the dark cycle and degrades during the light cycle. This result corresponds well to other studies on the rat SCN, in which a similar pattern of expression was discovered (Poirel et al. 2002; Neu and Niles 1997). Nevertheless, a study has reported contrary results with no significant change of MT1 receptor mRNA expression with time of the day in SCN (Sugden et al. 1999). Meanwhile, the expression of MT2 receptor is thought to be independent of the circadian rhythm. Waly and Hallworth (2015) did not find any circadian pattern of MT2 receptor in the SCN. Moreover, MT2, unlike MT1 receptor, is a receptor that desensitizes very rapidly in the presence of a full agonist of melatonin receptors (Witt-Enderby et al. 2003). Evidence from an *in vitro* study that used an MT2 selective antagonist to study the role of MT2 receptor in circadian rhythm is inconclusive (Hunt et al. 2001), mainly because it is not practical to study the circadian rhythm using *in vitro* techniques. Therefore, expression of MT1 receptor is strictly linked to circadian rhythm and SCN function, but not MT2 receptor. This is confirmed by studies on the KO animals—phase shift effect in sleep rhythm was not seen in the absence of MT1 receptor (Liu et al. 1997; Dubocovich et al. 2005), but it can occur in the absence of MT2 receptor (Weaver et al. 1996).

A particular effect melatonin has on the SCN is in sleep regulation, mainly in sleep promotion and sleep onset phase shift. The sleep/wake cycle is one of the many body rhythms regulated by the circadian system and is closely synchronized with the 24 h circulating melatonin level whose peak levels coincide with maximum sleepiness (Reiter et al. 2007). A study shows that MT1 receptor in the SCN mediates inhibition of neuronal firing, leading to promotion of sleep, as evidenced by MT1 KO mice demonstrating a reduction in rapid eye movement (REM) sleep (Ochoa-Sanchez et al. 2011). MT2 receptor, on the other hand, is implicated in the induction of sleep onset, mainly affecting non-rapid eye movement (NREM) sleep. MT2 KO studies revealed that NREM sleep was decreased while REM sleep remained unaffected in MT2 KO mice. This is supported by pharmacological studies using MT2 selective agonists, in which lengthened NREM sleep was observed (Comai and Gobbi 2014; Ochoa-Sanchez et al. 2011, 2014; Fisher and Sugden 2009). This indicates that MT2 receptor affects NREM sleep and the changes are related to the light phase of the light/dark sleep cycle (Comai and Gobbi 2014). In fact, sleep recordings in mice with genetic deletions of MT1, MT2 or both receptors have suggested that REM sleep is regulated by MT1 receptor,

whereas NREM sleep is largely regulated by MT2 receptor (Comai et al. 2013).

A study reveals that MT1 receptor colocalizes with vasopressin in neurons of SCN, parvocellular and magnocellular parts of PVN, with oxytocin in neurons of the SON, and with corticotropin-releasing hormone in neurons of the parvocellular part of PVN (Wu et al. 2006). The presence of MT1 receptor in these neurons suggests that perhaps melatonin is involved in the regulation of a few pituitary hormones. *In vitro* experiments using melatonin receptor ligands and receptor KO animals have shown that activation of MT1 and MT2 in the SCN, respectively, leads to distinctive responses. An *in vitro* study on rodent SCN slices showed that there is a concentration-dependent effect of melatonin on neuronal firing inhibition (Shibata et al. 1989). Further studies with targeted disruption of the MT1 receptor in transgenic mice revealed that the inhibitory action on neuronal firing in the SCN is absent in MT1 KO mice (Liu et al. 1997; Jin et al. 2003). These findings suggest that inhibitory effect on neuronal activity in the SCN is primarily mediated by the MT1 receptor. Meanwhile, an *in vitro* study using an MT2 selective antagonist, 4-phenyl-2-propionamidotetralin (4P-PDOT), found that the circadian phase shifting effect on neuronal firing was mediated by the MT2 receptor (Hunt et al. 2001). However, this effect does not seem to be solely regulated by the MT2 receptor as there is evidence of interactions between MT1 and MT2 receptors to result in this outcome. The phase shift effect, while still present in MT1 KO mice, is reduced compared to wild-type mice, indicating a possible role of MT1 receptors in phase shift within the SCN (Liu et al. 1997). The phase shifting effects on circadian rhythm is observed in animals lacking the MT2 receptor in the SCN hence it is likely that these effects are mediated by MT1 receptor (Weaver et al. 1996). Taking these together, phase shifting in the SCN is mediated mainly by the MT1 receptor.

Over the years, it is believed that dopaminergic neurons in the hypothalamus are well reserved in Parkinson's disease (PD) and thus is concluded that hypothalamus might not be a susceptible brain region in PD (Matzuk and Saper 1985). However, a very recent study has pointed out that this notion may not be fully representative because hypothalamic gray matter volume loss was observed in PD patients and this was significantly associated with the reduced serum melatonin level in PD (Breen et al. 2016). This reduced systemic level of melatonin was also seen in early PD (Breen et al. 2014), suggesting that reduced melatonin level may lead to the disruption of hypothalamic functions and results in sleep dysfunction, a commonly reported non-motor symptom in PD. Level of melatonin might serve as a potential biomarker in PD diagnosis.

Pituitary gland

Consistent with findings from animal studies (Lacoste et al. 2015; Klosen et al. 2002; Adamah-Biassi et al. 2014), MT1 receptor was identified to be the main melatonin receptor in the pituitary gland in the human brain (Wu et al. 2006; Williams et al. 1997; Weaver et al. 1993). The pars tuberalis (PT) within the pituitary expresses a high level of MT1 receptor (Adamah-Biassi et al. 2014). In the rat PT, MT1 receptor is mainly expressed in a subpopulation of endocrine cells which also expresses alpha-glycoprotein subunit and beta-thyroid-stimulating hormone (Klosen et al. 2002). Colocalization of MT1 receptor and retinoid-related orphan receptor beta (ROR beta) was reported in these cells (Klosen et al. 2002). It was speculated that melatonin possibly controls the transcriptional activity of ROR receptors indirectly via the MT1 receptor. ROR beta is a nuclear receptor belonging to the RZR/ROR family. It was once suggested that melatonin was an endogenous ligand to ROR beta based on a study using *in vitro* transient transfection assay (Becker-Andre et al. 1994). However, the authors failed to reproduce the results later. Therefore, it is still inconclusive whether melatonin is a native ligand to ROR beta in PT.

The neurocrine function of the pituitary gland is closely associated with the hypothalamus. MT1 receptor colocalizes with vasopressin, oxytocin, and corticotropin-releasing hormone-secreting neurons in the pituitary, respectively, suggesting a role of melatonin in regulating these pituitary hormones (see 5.6) although this functional link is not well understood (Wu et al. 2006). Interestingly, several reports have found that melatonin is also involved in regulating prolactin secretion (Williams et al. 1997; Jilg et al. 2005). In mammals, it is widely accepted that photoperiod changes alter patterns of pineal melatonin production, which results in changes of pituitary hormone secretion. In a study using hypothalamo-pituitary disconnected rams, binding sites of 2-[125I]iodomelatonin were unaltered compared to the control rams, but secretion of many pituitary hormones, except prolactin, was affected by the disrupted hypothalamus–pituitary axis. This shows that prolactin is regulated by melatonin rather than the hypothalamus–pituitary axis. Despite this finding, colocalization of the MT1 receptor with prolactin was not observed in the PT. Hence, it is postulated that melatonin acts on another site within the pituitary gland to control prolactin secretion and this action is independent of external influence. Later this site was identified to be the pars distalis (Jilg et al. 2005). This study also demonstrated that binding of melatonin to the MT1 receptor triggers the change of mRNA expression of a few circadian proteins such as *Per1*, *Per2* and *Cry1*, which ultimately results in the change of seasonal cycle in prolactin secretion. Furthermore, it was reported that

melatonin regulates expression of clock genes, particularly *Per1*, *Cry1*, *Clock*, and *Bmal1*, through the MT1 receptor (Dardente et al. 2003; von Gall et al. 2005). Interestingly, evidence yielded from an *in vitro* study using GT1-7 gonadotrophin-releasing hormone (GnRH) secreting neurons also suggests that melatonin might regulate gene expression of GnRH in the pituitary gland (Roy and Belsham 2002).

Periaqueductal gray

The antinociceptive effect of melatonin has been documented previously (Ambriz-Tututi et al. 2009). Melatonin is able to attenuate nociceptive responses to noxious stimuli such as heat, inflammation and neuropathic pain (Lopez-Canul et al. 2015a, b). This effect is often described as potent and longlasting in the animal model (Lakin et al. 1981). The periaqueductal gray in the midbrain is known to be involved in analgesia via the action of enkephalins on opioid receptors (Graeff 2012). The presence of melatonin receptors in the periaqueductal gray (mostly MT2 receptors, even if MT1 are also present), as evidenced by several animal studies, suggests that melatonin may play a pivotal role in pain processing (Lacoste et al. 2015; Lopez-Canul et al. 2015b; Adamah-Biassi et al. 2014). In fact, it has been reported that melatonin receptors, at least MT2, modulate antinociception via the glutamatergic pathway (Lopez-Canul et al. 2015b). This action of melatonin potentially results in the secretion of opioid peptide beta-endorphin but not enkephalin in the periaqueductal gray, which presumably leads to the analgesic effect (Yu et al. 2000).

Dorsal raphe nucleus

Moderate immunoreactivity of the MT1 receptor in the dorsal raphe nucleus (DR) has suggested the possible involvement of the MT1 receptor in the pathogenesis of depression (Lacoste et al. 2015). This is supported by a study which has demonstrated behavioral changes that mimic the symptoms of melancholic depression in MT1 KO mice (Comai et al. 2015). On top of that, there is evidence of melatonin imposing tonic inhibitory control over a subpopulation of serotonin-containing neurons in DR (Dominguez-Lopez et al. 2012). Changes in serotonin levels in DR have been implicated in mood disorders such as depression. Hence, this study has suggested a possible link between melatonin and serotonin neurotransmission in depression.

Midbrain

The striatum and substantia nigra are important in the production of movement. These two regions are connected through the nigrostriatal pathway, one of the main

dopaminergic pathways located within the brain. Several evidence has supported that melatonin may have a receptor-mediated role in the nigrostriatal dopaminergic pathways. First, mRNA expression for both MT1 and MT2 receptors has been observed in the striatum of mice, rats and human (Uz et al. 2003). Also, MT1 receptor is found in caudate–putamen and it colocalizes with D2 receptor (Uz et al. 2005). Furthermore, neuroanatomical mapping of rat's SN revealed a high level of the MT1 receptor in the SN pars compacta and the MT2 receptor in the SN pars reticulata (Lacoste et al. 2015). The presence of melatonin receptors in these regions implies the involvement of melatonin in the movement initiation process. It is likely that melatonin acts by inhibiting the secretion of dopamine via MT1 receptor in this pathway (Zisapel 2001). Abnormality in nigrostriatal dopaminergic pathway is heavily implicated in PD. There was a report that both melatonin receptors were found to be downregulated in the amygdala and SN of idiopathic PD patients (Adi et al. 2010). Along with the reported systemic changes of melatonin levels in PD patients (Bordet et al. 2003; Videnovic et al. 2014), this intriguing finding would indicate a possible involvement of melatonin in the progression of PD, although more studies are mandatory to confirm this association.

There is evidence that MT1, but not MT2 receptor, in striatum is involved in the pathophysiology of Huntington's disease (HD). In HD patients, mRNA and protein expression level of MT1, but not MT2 receptor, are decreased in the striatum (Wang et al. 2011). However, this deficit can be partially reversed by treatment with melatonin in R6/2 mouse model of HD (Wang et al. 2011). This mechanism by melatonin is likely mediated by blockage of mitochondrial cell death pathway. Hence, melatonin might confer neuroprotection in HD via MT1-mediated action.

On the other hand, melatonin receptor might be involved in the mesocorticolimbic projections too. Dopaminergic neurons in ventral tegmental area and nucleus accumbens express MT1 mRNA (Uz et al. 2005). In nucleus accumbens, MT1 receptor colocalizes with D2 receptor. These regions are central to the mesocorticolimbic dopaminergic system. The presence of the MT1 receptor in these areas suggests possible involvement of melatonin in the reward system, possibly via modulation of the dopaminergic system.

Meanwhile, there have been reports that suggest, instead of modulating the dopaminergic system, melatonin protects neurons against devastating conditions such as elevated oxidative stress in the dopaminergic neurons as depicted in studies on a PD model (Srinivasan et al. 2011; Saravanan et al. 2007). It is possible that melatonin confers neuroprotection via receptor-mediated actions in PD. Nevertheless, current evidence is too scarce and further functional research, such as KO studies, is required to warrant the exact roles of melatonin and its receptors.

Cerebellum

While consensus on the exact role of the cerebellum has yet to be reached, this region is heavily implicated in motor control, execution and learning and non-motor functions such as cognition (Manto et al. 2012; Buckner 2013). In situ hybridisation on human cerebellum revealed that MT1 receptor mRNA was expressed in granule cells and basket–stellate cells while MT2 receptor mRNA was found in Bergmann glia and astrocytes (Al-Ghoul et al. 1998). Presence of MT1 receptor in the cerebellum has also been confirmed in a transgenic mouse model (Adamah-Biassi et al. 2014).

Cerebellum plays a supporting role in various brain functions such as motor control and cognition. As such, elucidating the specific pathways regulated by melatonin receptors in this region has been difficult. One of the earliest correlations found between melatonin and the cerebellum was in balance control, where administration of melatonin impaired sensorimotor performance (Fraschini et al. 1999). Posture control relies on multisensory integration, which occurs mainly in the cerebellum. Administration of melatonin could have activated cerebellar melatonin receptors to lead to an inhibitory effect on cerebellar sensory integration or on pathways from the cerebellum to the vestibular system. One study has demonstrated the neuroprotective effect of melatonin on the cerebellum (Manda et al. 2008), which was abolished by the melatonin receptor antagonist luzindole. Moreover, melatonin upregulates the gene expressions of antioxidant enzymes catalase and superoxide dismutase in cerebellum in aluminum-treated mice (Esparza et al. 2005). While the exact pathways or melatonin receptor subtypes involved are yet to be elucidated, the findings indicate that the presence of melatonin receptors in the cerebellum may confer additional neuroprotection to that region. In a recent *in vivo* study by Pinato et al. (2015), the cerebellum was shown to be able to synthesize melatonin during acute neuroinflammation induced by intracerebroventricular lipopolysaccharide injection in male Wistar rats. This local production of melatonin induced by lipopolysaccharide was only observed in the cerebellum but not in the hippocampus and the cortex. The increase in cerebellar melatonin confers neuroprotection specifically to that region, where neuronal damage was less pronounced after lipopolysaccharide injection, compared to the hippocampus and the cortex.

Concluding remarks

In this review, we have discussed the distribution of melatonin receptors in the brain. Based on the fact that certain variation across species has been noticed for the location of melatonin receptors (Stankov et al. 1991), we

have only included findings from mammals for discussion in hope that these findings can be extrapolated to human. Though melatonin was discovered over half a century ago, its actions are still largely unknown. While melatonin receptors are abundant in the brain, their functions and underlying pathways remain unclear due to the complexity of the brain. With findings from a number of studies, we speculate that melatonin is an important mediator of a wide range of physiological functions, and alterations in the melatonin system are implicated in the etiopathogenesis of diverse neurodegenerative diseases such as AD, PD and HD. Therefore, future investigation on the actions of melatonin receptors in the brain should be warranted. Development of selective MT1 and MT2 receptor ligands should also be emphasized to facilitate studies of these receptors.

Acknowledgements This work is supported by MOSTI eScience Research Grant (02-02-10-SF0109) from Ministry of Science, Technology and Innovation of Malaysia.

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