Melatonin

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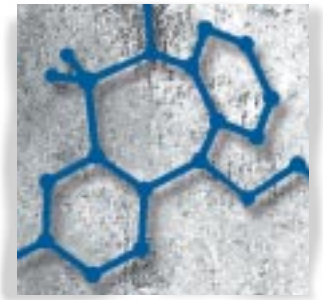

Melatonin (MEL) is a hormone synthesized and secreted by the pineal gland deep within the brain in response to photoperiodic cues relayed from the retina via an endogenous circadian oscillator within the suprachiasmatic nucleus in the hypothalamus. The circadian rhythm of melatonin production and release, characterized by nocturnal activity and daytime quiescence, is an important temporal signal to the body structures that can read it. Melatonin acts through high-affinity receptors located centrally and in numerous peripheral organs. Different receptor subtypes have been cloned and characterized: MT_1 and MT_2 (transmembrane G-protein–coupled receptors), and MT_3. However, their physiological role remains unelucidated, although livestock management applications already include the control of seasonal breeding and milk production. As for potential therapeutic applications, exogenous melatonin or a melatonin agonist and selective 5-hydroxytryptamine receptor ($5\text{-}HT_{2C}$) antagonist, eg, S 20098, can be used to manipulate circadian processes such as the sleep–wake cycle, which are frequently disrupted in many conditions, most notably seasonal affective disorder.

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Daily and seasonal rhythms in endocrine, physiological, and behavioral processes are a fundamental feature of all living organisms reflecting a need to ensure that biological functions occur at a given time of the day or year. The most obvious example is the fact that many animals are active only during the hours of daylight (diurnal species; human belong to this group) or the hours of darkness (nocturnal species), and are inactive during the other part of the day (sleep–wake cycle). Other rhythms, like hibernation, fur color changes, and migration, can also be given as examples.

In human, disruptions of rhythmicity are characteristic of, and may underlie, a variety of disorders. For example, sleep and circadian rhythms are often disrupted in neurological disorders, and increasing evidence indicates that alterations in the sleep–wake cycle accompany such neurological disorders. Moreover, delayed resynchronization to local time (jet lag) or with rotation of shift work is associated with general malaise (especially insomnia), a reduction in productivity at work, and an increase in numbers of accidents.

The challenge for scientists is to understand the functional mechanisms involved and to develop strategies to control or treat such disorders (eg, to accelerate resynchronization to new work schedules or to treat endogenous depression or sleep disorders).

The mechanism used for the daily or seasonal organization of functions is far from being well understood. Today, however, we know that this mechanism is built around three key components: (i) photoreceptors registering and transmitting environmental light cues; (ii) "clocks" that generate rhythms with a period of about 24 h and are capable of being entrained to exactly 24 h, especially by the light–dark (LD) cycle; and (iii) endocrine and neuroendocrine effectors receiving signals from the clock and translating them into a hormonal or neurohormonal response. Over the past few years, the huge surge in molecular biology has led to the identification of several clock genes (*Per1, Per2, Per3, Clock, BMAL1, Cry1, Cry2,* and *Caseine kinase* ε). These findings led to a molecular model of circadian oscillations based on two interlocking transcriptional/translational feedback loops.[1,2] The timing information built into the

Selected abbreviations and acronyms

4P-ADOT	*4-phenylacetamidotetraline*
cAMP	*cyclic adenosine monophosphate*
5-HT	*5-hydroxytryptamine (serotonin)*
LD	*light–dark*
MEL	*melatonin*
4P-PDOT	*4-phenylpropionamidotetraline*
PT	*pars tuberalis*
PTX	*pertussis toxin*
SCN	*suprachiasmatic nuclei*
SP	*short photoperiod*

clock, via nervous and endocrine pathways, is forwarded to specialized structures. Among these structures is the pineal gland, which secretes the hormone melatonin (MEL), whose role and mechanisms of action will be analyzed in this review.

Synthesis and production of melatonin

In 1917, McCord and Allen reported that bovine pineal extracts were potent frog skin lightening factors.[3] In 1958, Lerner et al isolated the agent responsible for the observed aggregation of melanophores, *N*-acetyl-5-methoxytryptamine, and termed it melatonin.[4]

The synthesis of MEL within the pineal gland is mainly regulated by the daily and seasonal changes in the environmental LD cycle. The synthesis of MEL is markedly increased at night in all species studied to date, independent of whether the animal is diurnally or nocturnally active, and the duration of the nocturnal peak is positively related to the duration of the night.[5,6] In nonmammalian vertebrates, the rhythmic synthesis and secretion of MEL is the direct output of the clock located within the pineal. In mammals, however, the pineal does not retain clock and photoreceptive properties. The synthesis of MEL is driven through multisynaptic neural pathways[7,8] by the circadian clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus, and is therefore also an output of the circadian clock.

MEL is synthesized from the amino acid tryptophan, which is first converted into 5-hydroxytryptophan by tryptophan hydroxylase, before being decarboxylated into serotonin (5-hydroxytryptamine, 5-HT). From 5-HT, two major enzymatic steps are involved. The first is N-acetylation by the arylalkylamine-*N*-acetyltransferase (AA-NAT) to yield *N*-acetylserotonin. The regulation of AA-NAT, with its sharp increase in activity at night, has received considerable attention as a major regulatory step in rhythmic MEL synthesis.[9,10] The second step is the transfer of a methyl group from 5-adenosylmethionine to the 5-hydroxy group of *N*-acetylserotonin catalyzed by the hydroxyindole O-methyltransferase (HIOMT), to yield MEL.[11] The rapid 6-hydroxylation of MEL in the liver means that it has a short half-life in the circulation and, therefore, the circulating MEL concentrations precisely reflect its pineal synthesis.

MEL is produced primarily by the pineal gland. However, numerous other MEL sources have been identified. The retina is an important source in nonmammalian vertebrates: not only is MEL rhythmically synthesized in this structure, but its release from here also contributes to the nocturnal pattern of circulating MEL. In mammals, MEL synthesis within the retina was demonstrated a long time ago.[12] However, it is only since the demonstration of a true circadian release of MEL from the hamster retina in vitro (suggesting the presence of a retinal clock) that the importance of this structure as an extrapineal source of MEL has been recognized.[13] In contrast to nonmammalian vertebrates, mammalian retinal MEL does not contribute to circulating MEL. The Harderian and lachrymal glands, gastrointestinal tract, red blood cells, platelets, and mononuclear cells have also been identified as sites of MEL synthesis. MEL does not seem to be released into the general circulation from these tissues, at least not under normal physiological conditions.[14] Moreover, in these tissues the synthesis of MEL is not rhythmic.

The presence of MEL is not restricted to vertebrates. MEL has been found in the head, eyes, optic lobe, and brain of various invertebrates in many taxa.[15] MEL has also been shown to be formed in fungi, plants, multicellular algae, and unicellular organisms.[16,17]

Sites of action of melatonin and signal transduction pathways

Before we start the description of present knowledge on the mechanisms involved, it should be mentioned that MEL has been reported to be a potent free-radical scavenger at high doses.[18] This pharmacological effect can be explained through direct scavenging of free radicals or through interactions with enzymes that improve total antioxidative defense capacity. This effect should not be

neglected when the therapeutic potential of the hormone is assessed,[19] especially because MEL has recently been demonstrated to bind to quinone reductase (QR2), an enzyme with well-known oxidoreductive properties.[20]

Whether MEL has autocrine or paracrine effects is also an important question. MEL might indeed act locally at sites where or close to where it is produced. This is probable, especially when extrapineal sources are considered. For example, in the retina, MEL is known to inhibit the release of dopamine.[21] The fact that enzymatic deacetylation of MEL occurs in the retina or brain of a variety of vertebrates,[22] along with the detection of low amount of *N*-acetyltransferase mRNA in tissues other than the pineal and retina,[9] also favors the concept of a local role for MEL. One could thus imagine an evolutionary sequence that starts with MEL being a local modulator within the cell or in neighboring cells (eg, light and dark adaptation in the retina, or food adaptation in the gut). The second step would involve the use of MEL as a hormone to control a variety of responses. Even though the local role of MEL may be common or universal, most of our knowledge concerns the role of MEL as a hormonal transducer of photic/photoperiodic information, and it is this aspect we will deal with.

As usual for many other hormones, MEL acts principally through specific protein receptors (see below). However the hormone's high lipophilicity enables it to penetrate all organs within the body, all structures within the brain, as well as all compartments within cells. Interactions with specific intracellular proteins like calmodulin or tubulin[23] have been reported and, even if our knowledge is still poor, this could also be part of the mechanisms involved.

Melatonin receptors

The first experiments on brain MEL receptors were carried out in the late 1970s.[24-26] The low reproducibility of the radioligand quality has prevented further development. It was the introduction of 2-[^{125}I]iodomelatonin ([^{125}I]MEL), first used as a ligand for MEL radioimmunoassay,[27] which opened the recent development of the MEL receptor field. This potent MEL receptor agonist, the first pharmacological tool available, led to the detection of high–specific activity binding sites, first on membrane fractions of whole rat brain[28] and then by auradiotography on rat brain sections.[29]

Initially, [^{125}I]MEL binding sites were classified on the basis of pharmacological and kinetic differences into two subtypes, ML-1 (now MT_1, MT_2, and Mel_{1c}) and ML-2.* The ML-1 binding site has high-affinity MEL receptors (K_d<200 pM) with a consensus rank order of drug potency in inhibiting [^{125}I]MEL binding as follows: 2-iodomelatonin > 6-chloromelatonin ≥ MEL > 6-hydroxymelatonin > *N*-acetylserotonin >> 5-hydroxytryptamine. The ML-2 binding sites are characterized by a K_d in the nanomolar range with a distinct pharmacological profile, notably a similar affinity for MEL and *N*-acetylserotonin.[33,34] Due to difficulties in their characterization and to their low affinity, which does not seem to be compatible with the circulating MEL levels, less attention had been given to these ML-2 binding sites. The recent identification of MT_3 receptor reopens this question (see below).

Molecular identification of MEL receptor subtypes

The cloning of the first high-affinity MEL receptor was a landmark in MEL receptor research history. This was achieved by using an expression cloning strategy to isolate the complementary DNA encoding for MEL receptor of *Xenopus laevis* dermal melanophores.[35] This *Xenopus* MEL receptor cDNA encoded a protein with seven putative transmembrane regions that led to its classification within the superfamily of G-protein–coupled receptors.[35] Identification of the *Xenopus* receptor sequence using homology-based screening methods led to the subsequent identification of three types of vertebrate MEL receptors. Two receptor subtypes with high-affinity for MEL (initially termed Mel_{1a} and Mel_{1b}, but now called MT_1 and MT_2) have been cloned and characterized from sheep pars tuberalis (PT), human SCN and hamster and rat hypothalamus.[36,37] In sheep PT, allelic isoforms of MT_1 receptors (termed $Mel_{1a(\alpha)}$ and $Mel_{1a(\beta)}$, respectively) have been identified.[38] A third subtype of high-affinity MEL receptor was cloned from a chicken brain library and termed the Mel_{1c}.[39] The first *Xenopus* receptor to be isolated was a Mel_{1c} receptor, which exists in two allelic isoforms, $Mel_{1c(\alpha)}$ and $Mel_{1c(\beta)}$. So far, no mammalian homologue of the Mel_{1c} receptor has been isolated, but cDNA fragments for a nonmam-

* These classifications come from the Nomenclature Committee of the IUPHAR.[30-32] IUPHAR nomenclature does not include receptors found in nonmammalian species, which explains the terminology Mel_{1c}. The older terminology ML-1/ML-2 should not be confused with the new one. MT_1, MT_2, and Mel_{1c} correspond to ML-1; the old ML-2 is now called MT_3.

malian Mel_{1b} have. All this molecular work has also demonstrated that the characteristics of the high-affinity receptors are present in each of the three related receptors (MT_1, MT_2, and Mel_{1c}).

Very probably this is only the beginning of a long list. A receptor structurally related to the MEL receptors has already been isolated[40,41] with a very interesting distribution of expression in neuroendocrine tissues.[42] The natural ligand for this receptor has not been identified (could it be a MEL metabolite?). More recently, a MEL receptor with a nanomolar affinity, called MT_3, has also been isolated. The MT_3 site is not a G-protein–coupled receptor, but corresponds to a binding on the enzyme quinone reductase.[20] Moreover, considering the lipophilic nature of hormone, the probability of a nuclear site of action of MEL is very high, and such a site will be identified one day soon.

Localization of melatonin receptors

Since 1987, the use of [^{125}I]MEL as a ligand with a high specific activity has permitted studies on the localization of MEL receptors (or more exactly binding sites) of the MEL-1 family (MT_1, MT_2, and Mel_{1c}). The binding sites appear to be widespread in vertebrates. Comparative distribution studies reveal the presence of MEL binding sites in the brain of five vertebrate classes (fish, amphibian, reptiles, birds, and mammals). The most relevant feature is that the distribution of MEL binding sites in lower vertebrates is much larger than in mammals, and they are consistently found in areas associated with retinorecipient and integrative structures of the visual system.[43] In mammals the situation is more contrasted. Contrary to what is generally claimed, in mammals, MEL receptors are also present in a large number of structures. They have been described in more than 110 brain structures, among them the internal granular layer and the external plexiform layer of the olfactory bulb, lateral septum, septohippocampal nucleus, caudate putamen bed nucleus of the stria terminalis, SCN, mediobasal hypothalamic nuclei, paraventricular nuclei of the hypothalamus, paraventricular nuclei of the thalamus, intergeniculate leaflet, central and medial amygdaloid nucleus, inferior colliculus, fasciculus retroflexus, substantia nigra, and frontal, orbitofrontal, and parietal cortex.[44-46] However, a great variability has been noted in the number and location of labeled structures among the species, as well as large differences in receptor density between structures and in the same structures between species. Few structures are common, even among species from the same family,[44] and very probably this should be correlated either to the numerous photoperiodic responses, which are different from one species to another, or to the many different effects described for MEL (see below).

Among all these structures, the pituitary PT, which shows the highest density of MEL receptors and is the only structure found consistently labeled in all mammals so far studied, and the SCN, which contains MEL receptors in many species, are considered as two major sites for MEL action (see below). However, it should also be pointed out that MEL receptors/binding sites have been identified in numerous peripheral organs. The role of these receptors has not yet been extensively studied, but their presence explains the reported direct action of MEL, for example, on blood vessels[47-49] and on cell-mediated and humoral immune function[50] on Leydig and luteal cells.[51] Its also indicates that the MEL message can be read at different levels of the organism, which should be taken into account when the potential therapeutic properties of MEL or MEL analogues are considered, especially as specific binding sites have been reported in several neoplastic tissues.[52,53]

The availability of new molecular tools following the cloning of different subtypes of MEL receptor has permitted a more precise analysis of their distribution. Using in situ hybridization, it was shown that the MT_1 receptor mRNA is, in rodents, present within the SCN, paraventricular thalamus, and PT.[54] The MT_2 subtype seems to be mainly expressed in the retina (also in hippocampus),[31,32,37,55] where its expression is linked with the well-known MEL-induced inhibition of dopamine release. Its expression in the SCN is not yet clarified. MT_2-specific oligonucleotides were reported to generate a signal in mice SCN by nonradioactive in situ hybridization,[32] but using a 0.6-kb long riboprobe, Poirel et al[56] were unable to detect any signal by in situ hybridization within the rat SCN. Moreover, 4-phenylpropionamidotetraline (4P-PDOT) and 4-phenylacetamidotetraline (4P-ADOT), two molecules that specifically displace 2-iodomelatonin binding from MT_2 binding sites expressed in transfected cells, do not displace 2-iodomelatonin binding in the SCN.[55] As targeted molecular disruption of the MT_1 receptor in mice resulted in the total disappearance of 2-iodomelatonin binding in brain tissues including the SCN, it seems that

the well-described SCN 2-iodomelatonin binding sites are translated from MT_1 mRNA.
However, although it is difficult to detect MT_2 receptors in the SCN, either by their pharmacological binding profiles or by their mRNA expression, the two known antagonists of this receptor subtype (4-PDOT and 4P-ADOT) appear to have a functional effect on the SCN circadian clock and inhibit in vitro the MEL-induced phase advance of SCN activity.[32] These apparently discrepant data suggest the involvement of a third receptor subtype expressed in the SCN and binding MEL and 4P-PDOT/4P-ADOT with high affinity, but 2-iodomelatonin with low affinity. As the phase-shifting response in MT_1-deficient mice is blocked by pertussis toxin (PTX),[55] this receptor subtype would be also a G-protein–coupled receptor.

Signal transduction

The major bioassays that have been used to determine signal transduction are as follows: the condensation of pigment granules in the melanophores of amphibians[57]; the inhibition of calcium-dependent electrical field–stimulated ^{3}H-dopamine release from rabbit retina[34]; the second messenger changes in ovine PT[58,59]; the hormonal secretion in neonatal pars distalis of rats[60]; the acute inhibition and phase shift of neuronal firing in rat/mouse SCN slices in vitro; and the vascular vasoconstriction in rat tail artery.
In amphibian dermal melanophores, MEL affects melanin movement through a PTX-sensitive G-protein,[61] and the pineal hormone decreases cyclic adenosine monophosphate (cAMP) accumulation.[62] The same signaling pathway is used in PT.[59] MEL indeed has no effect on the basal level of cAMP in the PT of hamster and sheep, but inhibits forskolin-induced cAMP accumulation,[59,63,64] as well as forskolin-induced phosphorylation of the transcriptional activator cAMP-responsive element binding protein (CREB).[64,65] This effect of MEL is PTX sensitive, indicating coupling of the receptor to a G_i-protein.[63,64] However, a cholera toxin–sensitive component also mediates the inhibition of forskolin-stimulated cAMP accumulation,[58] implying coupling through a G_o-protein. Interestingly, pretreatment with MEL results in a sensitization of adenylate cyclase, and a potentiated cAMP response to forskolin stimulation.[66,67]
In the neonatal rat anterior pituitary, MEL has effects on numerous signal transduction pathways (inhibition of cAMP and accumulation of cyclic guanosine monophosphate [cGMP], suppression of diacylglycerol synthesis and arachidonic acid release, decrease in intracellular Ca^{2+} concentration, and increase in membrane potential).[60,68] MEL has also been reported to influence the phospholipase C and the diacylglycerol-mediated activation of the protein kinase C.[31,69]
The cloning of MEL receptor cDNA has permitted the development of cell lines in which either MT_1 or MT_2 recombinant receptors are expressed. It is thus possible to link specific MEL receptor subtypes with specific signal transduction responses. Functionally, when the cloned receptor subtypes (hMT_1 and hMT_2) are expressed in the different cell lines tested (COS-7, NIH-3T3, CHO, human HEK293, human HeLa, and murine Ltk cells), they inhibit forskolin-stimulated cAMP accumulation, confirming the coupling of MEL receptors to this transduction pathway, as previously observed in tissues. Moreover, studies with heterologous expression of mammalian MEL receptors have helped characterize additional signal transduction pathways. In short, activation of recombinant human MT_1 receptors elicits multiple cellular responses that are mediated by both PTX-sensitive and PTX-insensitive G-proteins. Not only is the inhibition of forskolin-induced cAMP accumulation observed,[70-72] but a potentiation of the prostaglandin $F_{2\alpha}$–induced release of arachidonate and hydrolysis of phosphoinositide is noted.[70] The functional significance of this differential G-protein coupling was further deciphered: G_{i2}- and G_{i3}-proteins mediate adenylyl cyclase inhibition through a PTX-sensitive mechanism, while the PTX-insensitive $G_{q/11}$-protein is coupled to phospholipase Cβ activity. Furthermore, activation of the MT_1 receptor induces a transient elevation of cytosolic calcium ion concentration and an accumulation of inositol phosphate.[71,72]
The recombinant MT_2 receptor is also coupled to inhibition of adenylyl cyclase activity by a PTX-sensitive G-protein.[37] Additionally, activation of the recombinant MT_2 receptor specifically inhibits cGMP levels via the soluble guanylyl cyclase pathway.[73]
What does this multiplicity of MEL effects mean for MEL receptors in vivo? Heterologous overexpression reveals the potential to couple to a specific signal transduction pathway only. For in vivo work, this should be interpreted in the context of pathways identified in each specific tissue. For more details, we refer to recent review articles by Masana and Dubocovich[74] and von Gall et al.[75]

Pharmacology

The different cloned MEL receptor subtypes that are required to perform specific functions possess intrinsic differences. This is evident in terms of both the cell tissue distribution and the signal transduction pathways involved. Over the next few years, the identification of the links between specific target sites for MEL, specific MEL receptor subtypes, and particular physiological actions will be a great challenge. For this, many more pharmacological investigations are required. There is especially a great need for selective agonists and antagonists.

Many such pharmacological studies have been done[31,32,45,57] and are still performed in native tissue models, especially ovine PT cells and amphibian melanophores. Advances in the molecular biology of MEL receptor subtypes, however, have permitted the development of gene cloning and expression technologies. Different cell lines (COS-7, NIH-3T3, and CHO) expressing high levels of specific recombinant receptors (either hMT_1 or hMT_2) provide the means for a rapid characterization of receptor-mediated ligand binding and functional responses.

Numerous agonists and antagonists have been developed and are already available *(Tables I and II)*[34,57,46,76-92] and the further development in the engineered cell systems will quickly increase this number. In addition to their usefulness as pharmacological tools for studying the physiological role of MEL receptor subtypes, they have started to be tested for clinical applications mostly for circadian-based disorders. However, presently, in all recombinant systems used, no MEL receptor agonist with a rate of selectivity over 100 for MEL receptors subtypes in intact tissues is currently available.[80] However, some partial agonists or antagonists have selectivity above 100 and could be considered as selective MT_2 analogues, and thus be used to distinguish the MT_2 from MT_1 receptors in mammalian tissue.

Role of melatonin

Melatonin and seasonal functions

Environmental lighting acting through the eyes in mammals has a profound effect on the rhythm of MEL synthesis. The duration of the peak of MEL secretion is positively correlated with the length of the night. It is through these changes in duration of MEL synthesis that the brain is able to integrate photoperiodic information. This explains the present use of this hormone in farming to control seasonal functions (eg, fur growth, reproduction, and milk production). This also opens therapeutic prospects if we consider the hypothesis of Wehr[93] "that the photoperiod-induced changes in the duration of MEL secretion drive the annual cycle that occur in seasonal affective disorders." The exact mechanism of action of MEL is unclear. The duration of nocturnal MEL production is the key signal,[5] but the existence within this signal of a MEL-driven circadian rhythm of sensitivity to MEL has been proposed to explain the photoperiodic response.[94] The MEL receptors involved are most probably of the MT_1 subtype. Indeed, the gene of the only other MEL receptor subtype found in mammals, MT_2, is nonfunctional in two highly photoperiodic species, Siberian and Syrian hamsters. The target sites mediating the MEL control of the photoperiod-dependent seasonal functions and especially the annual sexual cycle have not yet been totally determined. One structure, however, the pituitary PT, which contains a very high density of MEL receptors in all mammals studied is thought to be of primary importance. Its density in MEL receptors exhibits clear seasonal changes in seasonal species, but not in nonphotoperiodic mammals,[95,96] and its implication in the control of seasonal secretion of prolactin has been demonstrated.[97-99] The PT has already been used to delineate the MEL's signal transduction pathways (see above) and thus appears to be a good model to study how the cellular response can distinguish between long- and short-duration MEL signals. The cAMP-mediated pathways appear to be central to the MEL readout. Pretreatment with MEL has been demonstrated to induce a sensitization of adenylate cyclase, and a potentiated cAMP response to forskolin stimulation.[66,67] MEL pretreatment to potentiate cAMP accumulation in the PT is duration dependent (between 0-16 h) and corresponds well with the duration of the nocturnal MEL signal.[66]

Most probably, the integration of the photoperiodic message throughout the change in the duration of the MEL signal in a given structure will depend on altered levels of expression of specific genes in that structure. The most likely route by which this could be achieved is through MEL's effect on transcription factors. Several cAMP-responsive genes, including the transcriptional inhibitor inducible cAMP early repressor (*ICER*) and the clock gene *Per1* are rhythmically expressed in the PT. The nocturnal MEL signal is crucial for the rhythmic

Agonists	**Receptor(s)**	**Reference**
AH-001 (2-acetamido-8-methoxytetralin)	MT_1/MT_2	76
AH-017 (2-chloroacetamido-8-methoxytetralin)	MT_1/MT_2	76
AMMTC (*N*-acetyl-4-aminomethyl-6-methoxy-9-methyl-1,2,3,4-tetrahydrocarbazole)	$MT_1/MT_2/Mel_{1c}$*	77
	MT_1/MT_2†	78
2-Bromomelatonin	MT_1/MT_2	79
2-Chloromelatonin	$MT_1/MT_2/ Mel_{1c}$	80
6-Chloro-2-methylmelatonin	MT_1/MT_2	80
6-Hydroxymelatonin	MT_1/MT_2‡	81
	MT_1/MT_2†	78
GG-012 (4-methoxy-2-(methylene propylamide)indan)	Partial MT_1/MT_2	76
GR 128107 (3-(1-acetyl-3-methylpiperidine)-5-methoxyindole)	Partial MT_1/MT_2§	82
GR 196429b (1-[2-(*N*-acetyl)aminoethyl]-7,8-dihydrofuro[2,3-γ]-2,3-dihydroindole·HCl)	MT_1/MT_2	76, 83
	MT_1/MT_2‖	84
HEAT (5-hydroxyethoxy-*N*-acetyltryptamine)	MT_1	85
IIK7	MT_2§	86
2-Iodomelatonin	$MT_1/MT_2/Mel_{1c}$	87
8M-ADOT (8-methoxy-2-acetamidotetralin)	MT_1/MT_2	80
8M-PDOT (8-methoxy-2-propionamidotetralin)	MT_1/MT_2	80
5-MCA-NAT (5-methoxycarbonylamino-*N*-acetyltryptamine)	MT_3	80
6-Methoxymelatonin	MT_1/MT_2‡	80
5-Methoxyluzindole	MT_3	80
	Partial MT_2‡	80
ML23 (*N*-(3,5-dinitrophenyl)-5-methoxytryptamine)	MT_1/MT_2	34,57
N-Acetylserotonin	MT_2	80
	Partial MT_1/MT_2‡	80
4P-PDOT (4-phenyl-2-propionamidotetraline)	Partial MT_2‡	81
	Partial MT_2¶	88
S 20098 (*N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide)	$MT_1/MT_2/ Mel_{1c}$	46,83,89
	MT_1#	90
	Partial MT_2#	90
S 20642	Partial MT_1#,**	90
	Partial MT_2#	90
S 22029	MT_1#	90
	Partial MT_2#	90
S 22365	MT_1#	90
	Partial MT_2#	90
S 22480	Partial MT_1#	90
	Partial MT_2#	90

Table I. Melatonin receptor agonists. Specific and currenty used molecules are presented in bold. Agonist are considered as specific when the MT_1/MT_2 or MT_2/MT_1 ratio obtained in recombinant melatonin receptors is >100. *On dopamine release in retina; †on tail artery; ‡in COS-7 cells expressing recombinant hMT_1 or hMT_2; §in NIH-3T3 cells expressing recombinant hMT_1 or hMT_2; ‖in CHO cells expressing recombinant hMT_1 or hMT_2; ¶inhibition of leuckocyte rolling in the microcirculation; #in HEK293 expressing recombinant hMT_1 or hMT_2; **in ovine pars tuberalis tissues.

expression of these genes.[100-103] *Per1* mRNA levels in the PT rise shortly after the dark-to-light transition,[103-105] immediately after the decline of the nocturnally elevated MEL signal. *Per1* mRNA accumulation is followed 6 h later by an elevation in nuclear *Per1* protein levels.[106,107] Removal of the pineal gland abolishes rhythmic PT gene expression, and extension of the dark phase of the lighting cycle dampens the amplitude of *Per1* and

Antagonists	Receptor(s)	Reference
DH97 (*N*-pentanoyl-2-benzyltryptamine)	MT_2	86
GR 135533	Mel_{1c}	86
GR 128107 (3-(1-acetyl-3-methylpiperidine)-5-methoxyindole)	MT_2	80
HEAT (5-hydroxyethoxy-*N*-acetyltryptamine)	MT_2	85
KI85	MT_2	86
Luzindole (2-benzyl-N-acetyl-tryptamine)	$MT_1/MT_2/Mel_{1c}$	80,86,90
	$MT_2>MT_1$	80
4P-ADOT (4-phenyl-2-acetamidotetraline)	MT_2	80
4P-CADOT (4-phenyl-2-chloroacetamidotetraline)	MT_2	80
4P-PDOT (4-phenyl-2-propionamidotetraline)	MT_2	80
	$Mel_{1c}^{\#}$	86
S 20928 (*N*-[2-(1-naphthyl)ethyl]cyclobutylcarboxamide)	MT_1/MT_2	91
	$MT_1^{\#,**}$	92
S 20642 (*N*-[2-(7-methoxy-1-naphthyl)ethyl]cyclobutylcarboxamide)		
S 20929	$Mel_{1c}^{\#}$	86
S 22153	MT_1/MT_2	83,92

Table I. Melatonin receptor antagonists. Specific and currently used molecules are presented in bold. Antagonists are considered as specific when the MT_1/MT_2 or MT_2/MT_1 ratio obtained in recombinant melatonin receptors is >100. #In HEK293 expressing recombinant hMT_1 or hMT_2; **in ovine pars tuberalis tissues.

ICER expression in PT cells.[102,103,106] What is the biological significance of *Per1* and *ICER* expression in the PT? The unique sensitivity of *Per1/ICER* expression to MEL in the PT suggests that these genes may be intrinsic to the MEL readout mechanism.[107,108] The complete understanding of the MEL/photoperiodic readout requires a link with the identified downstream response in the PT. This is still difficult. The PT has indeed been demonstrated to relay photoperiodic/MEL information to lactotroph cells in the pituitary through production of a prolactin-releasing (or release inhibitor) factor. This factor, termed "tuberlin,"[67,99] has not yet been identified.

Photoperiod-induced changes in prolactin secretion, however, are not enough to explain the annual sexual cycle. This implies that to mediate photoperiodic information MEL must act on other target sites. This multisite of action concept is supported by the observation that a long-duration MEL infusion, which mimics short photoperiod (SP), in hamsters with lesions of the dorsomedial hypothalamus is unable to induce a decrease in luteinizing hormone levels, while the prolactin levels decrease normally.[109,110] Moreover, in the sheep, MEL implants in the mediobasal hypothalamus block the effects of SP on luteinizing hormone but not on prolactin, while implants close to the PT inhibit prolactin secretion.[111] Interestingly, in hamsters, MEL binding sites have been detected in the dorsomedial hypothalamus (although at a very low density) and their density depends on the photoperiod (author's laboratory, unpublished data).

This hypothesis of a parallel and concomitant action of MEL on different structures to transduce the photoperiodic message is very attractive. Via changes in duration of MEL secretion, the photoperiod is known to control not only the annual reproductive cycle, but also a large number of other seasonal functions (eg, hibernation, daily torpor, fur color changes, migration, etc). Considering that not all these functions are expressed in all species and that, even when a given function is expressed, the control mechanisms involved are very different from one species to another (eg, SP induces an activation of the sexual axis in sheep but an inhibition in Syrian and Siberian hamsters; hibernation depends directly on photoperiod in the Syrian hamster, while in the European hamster it depends on a "circannual clock" [itself entrained by photoperiod]), it is probable that MEL acts on different structures depending on the species and the function. This concept explains the large interspecies differences in the distribution of MEL receptor–containing structures observed in mammals. In regard to photoperiodic responses, results obtained with the various MEL receptor antagonists should be considered. The antagonist S 20928 has been shown to block the SP-induced body

mass increase and to increase basal metabolism in the garden dormouse.[112] S 22153 is a MEL ligand characterized as a putative MEL antagonist of MT_1 and MT_2 MEL receptor subtypes,[92] which blocks the phase-shifting effect of MEL in mice,[83] the behavioral changes in mice induced by short-day exposure,[113,114] and the potentiation induced by MEL of electrically evoked contraction of isolated rat tail arteries. S 22153 appears to be able to differentiate different photoperiodic responses, at least in the Syrian hamster: it decreased the total hibernation duration observed in animals exposed to SP and low temperatures, and significantly inhibited the increase in interscapular brown adipose tissue mass. However, neither the gonadal atrophy nor the body mass increase induced by SP was affected by S 22153 (author's laboratory, unpublished data). To our knowledge, this is the first demonstration of a pharmacological dissociation of photoperiodic-controlled seasonal functions. Through changes in duration of its nocturnal peak, MEL can also distribute the photoperiodic message to all peripheral structures containing MEL receptors, which explains the increase in immunity observed under SP conditions in some species.

Melatonin and circadian functions

The diurnal organization of physiological processes relies on endogenous circadian oscillator(s) that generate rhythms and are capable of being entrained to cyclic environmental factors (eg, LD cycle). Such clocks convey circadian information to the rest of the organism via nervous and/or endocrine pathways. In most nonmammalian vertebrates, the rhythmic synthesis and secretion of MEL is the direct output of such clocks and the rhythmic changes in the concentration of circulating MEL are fundamental to circadian rhythmicity.[115] In mammals, it is generally assumed that the pineal gland is not involved in the generation and maintenance of circadian rhythmicity. Pinealectomy indeed appears to have little effect on the circadian rhythm of activity.[116] Therefore, it was concluded that, contrary to nonmammalian species, circulating rhythmic MEL had a very limited role in circadian organization. The MEL rhythm, however, is only one of the efferent signals of the clock. It is probable that for the circadian organization of functions, circadian information is distributed via a number of different efferent clock signals. Pinealectomy has little effect on circadian organization, perhaps because, even without MEL, the circadian signal can be integrated through other clock outputs.[117,118] This will not preclude an important role for MEL in circadian organization. Subtle desynchrony of several physiological functions after pinealectomy has been described[119] and the reentrainment of rat locomotor activity rhythm is modified after a phase-shift of the LD cycle.[120] One week after pinealectomy the firing rate rhythm of SCN neurons in vitro is altered, as well as the daily rhythm of responsiveness to MEL.[121] MEL is also known to interfere with metabolic activity (glucose utilization and protein synthesis) of the SCN.[122]

In addition, because the synthesis of MEL is under SCN control, the SCN may use the daily MEL signal to distribute the circadian message to any system that can "read" it, ie, to any structure or organ possessing MEL receptors, either in the central nervous system or in the periphery.[6,123] This concept explains many observations in the literature: MEL (or the MEL agonist and selective $5\text{-}HT_{2c}$ antagonist S 20098) inhibition of spontaneous and light-evoked activity of cells in the intergeniculate leaflet)[91]; MEL-enhancing splenic lymphocyte proliferation (attenuated by the antagonist luzindole)[50,124]; MEL-induced inhibition of leucocytes rolling and adhesion to rat microcirculation[88]; MEL-induced vasoconstriction of cerebral and tail arteries[49]; and the regulation of emotional behavior by MEL.[113,114] What could be the mechanism involved? Clock gene expression is widespread in mammalian tissues, but does not exhibit cell-autonomous self-sustaining rhythmicity, except in the SCN and the retina. Rather, it appears that cyclical expression in the periphery is driven by the SCN. The role of MEL in regulating rhythmic clock gene expression in peripheral tissues as described in the PT (see above) may be one of the mechanisms for tissue-specific regulation of the phase of rhythmicity. Interestingly, in rat PT, it has been demonstrated that the circadian rhythm of MEL receptor density is suppressed after pinealectomy and MEL drives this rhythm directly.[125,126]

Most of the results described above concern the role of endogenous MEL. As regards the potential therapeutic use of MEL or MEL derivatives, the effect of exogenous MEL must also be considered.

Chronobiotic properties of melatonin

A chronobiotic effect means that exogenous MEL can influence, directly or indirectly, the phase and/or the period of the circadian clock. In term of therapeutic

applications, this means that exogenous MEL (or a MEL agonist and selective 5-HT_{2c} antagonist such as S 20098) can be used as a pharmacological tool to manipulate sleep–wake cycle and other circadian rhythms. For a long time, it has been known that administration of MEL can entrain free-running activity rhythms in rodents.[43,127] For example, Redman et al[128] demonstrated that daily subcutaneous injections of MEL to rats strongly affect the locomotor activity rhythm. MEL and some agonists entrain the free-running locomotor activity rhythm of animals and entrainment only occurs when the MEL injection time coincides with the onset of activity. If the injection is given at any other time, the rhythm continues to free-run until this coincidence occurs. However, all these experiments[43,128] were based on bolus administration of MEL. Behavioral arousal (1–4 h before activity onset[129,130]) is known to induce a phase advance of the locomotor activity rhythm in Syrian hamster. Consequently, the arousal associated with the injection-induced daily handling of the rats may also interfere with the results. In support of this idea is the fact that a small percentage of the control animals became entrained to vehicle administration in the early experiments.[128]

In order to analyze the direct action of exogenous MEL on circadian organization, we consider it necessary to administer MEL in such a way that it does not by itself induce entrainment and to eliminate the nonspecific disturbance of the animals. MEL administration via timed access to drinking water has been shown to be an efficient way to entrain free-running activity rhythms in the rat: the entrainment occurs at the same circadian phase and with the same phase angle to MEL onset.[131] However, like the bolus administration experiments, this technique does not allow precise control of the duration of the peak MEL signal. The duration of MEL is known to provide essential information, at least in photoperiodic terms. To address these points, a chronic infusion device has been developed, which allows the animal freedom of movement in its cage and provides continuous drug infusion (over several months) of controlled duration and dose without handling.[132,133]

Daily infusions of MEL for 1, 8, or 16 h, or twice 1 h entrained the circadian rhythms of core body temperature, running-wheel activity, and general activity to 24 h. Nevertheless, regardless of the dose, the efficiency of MEL infusion decreased if it lasted a long time (16 h). During entrainment, when the intrinsic period of the circadian pacemaker is equal to the period of the Zeitgeber (or synchronizer), it is assumed that the pacemaker maintains a constant phase relation with the Zeitgeber. With daily injection or oral administration of MEL, the onset of activity is linked to the time of administration and the phase angle is close to zero. When MEL is administered by daily infusion, the phase angle difference between the entrained rhythm and the Zeitgeber (MEL) depends upon the duration of the infusion period. A negative phase angle is observed and its value increases with the duration of the infusion period. In addition to the effects on phase angle, another response has been observed. With an 8-h infusion and more evidently with a 16-h infusion, MEL administration induced a change in the free-running period in the first days. The period was lengthened compared with the saline infusion, suggesting that MEL delays the pacemaker each day until entrainment occurs. In other words, with a long duration of infusion, entrainment occurs earlier than predicted by the model based on the MEL injection experiments. Moreover, the magnitude of the change in period increased significantly with the duration of that infusion. These observations cannot be explained on the basis of a sensitivity window, but rather suggest that the chronobiotic properties of MEL imply an active mechanism on the circadian clock. This conclusion is supported by the results obtained after a "skeleton" infusion; two 1-h infusions with an interval of 15 h, corresponding to the extremities of the 16-h infusion. Under these conditions, MEL induced entrainment after a time during which circadian periods were either lengthened in a fraction of the animals or shortened in the others. However, all animals responded in such a way that, once entrained, their active phase occurred in the shorter time interval between the MEL signals. This finding suggests that to achieve entrainment, MEL has to induce either a phase delay (when the period was shortened) or a phase advance (when the period was lengthened). Such a dual effect of MEL has also been reported in other studies. For example, when rats experience a 5-h phase advance of the dark onset in LD conditions, those injected daily at the new dark onset reentrained with a decreased latency, some of the animals did so by phase delays, whereas others did so by phase advances.[134] Infusion of MEL has been reported to entrain hamsters or *Arvicanthis ansorgei,* a diurnal rodent, by inducing phase advances when the free-running period was longer than 24 h and phase delays when

the period was shorter than 24 h.[132,135] All these observations strongly suggest that the effects of exogenous MEL depend on the period before entrainment.

Does melatonin cause "true" entrainment?

Entrainment means that the period of the observed rhythm must adjust to and equal the Zeitgeber cycle (T), and a stable phase relationship must be established between the rhythm and Zeitgeber cycle.[136] According to the nonparametric model of entrainment, this synchronization process occurs through daily phase shifts, with the size and direction of shifts defined in the phase–response curve (PRC).[137] This has been demonstrated by experiments using light as a synchronizer and little is known about the synchronizer properties of MEL and, for example, the limits of entrainment to MEL are not yet well defined. In a recent study, Slotten et al[138] have studied this problem by administering MEL for a series of T values. The results indicate that the limiting phase-advance value, to which the rat activity rhythm entrains to MEL infusion, is approximately 35 min. Entrainment occurred at about circadian time (CT) 12; thus, at this phase of the activity cycle, MEL infusion induced the phase advance necessary to entrain the rhythm. The maximal daily phase-shift values defined by the MEL PRC[139] and the magnitude of phase-shift responses to a single MEL injection[140] ranges from 15 to 52 min. The entrainment limits found in this study correspond quite well to these maximal phase-advance values. We can thus conclude that in the rat, daily acute MEL administration causes "true" entrainment as defined by Enright.[141] Until now, such experiments have never been replicated with a MEL agonist.

Sites of action for the chronobiotic effects of melatonin

In all the experiments reported above, the responsiveness to MEL is restricted to a narrow window of sensitivity, which is generally late in the subjective afternoon, but depends upon the duration of the MEL signal as well as the previous free-running period. The finding that pinealectomized rats entrain to daily MEL administration[133,140] indicates that endogenous MEL is not necessary for the entrainment effect of exogenous MEL, for example, by entraining a window of sensitivity to MEL.[94] Nocturnal MEL production is a direct output of the SCN circadian clock. Exogenous MEL is effective at a time when endogenous MEL is not produced or present in the general circulation. Consequently the effects of MEL administration in vivo, as important as they are in terms of potential clinical applications, appear not to be related to the role of endogenous MEL on circadian functioning. This conclusion is reinforced by the observation that to obtain entrainment of the circadian activity rhythm of rodents kept under constant darkness, high doses of MEL have to be used, independently of the mode of administration.[131,133,142] These doses of MEL produce peak serum levels 100- to 1000-fold higher than the endogenous MEL nighttime levels. The necessity of such a high dose of MEL is unlikely to be a consequence of its rapid metabolism. Appropriate photoperiodic response is, indeed, obtained when MEL is administered via a similar subcutaneous infusion system with a dose that mimics the endogenous secretion profile.[94,143] Most likely, this high dose of MEL is needed because it is an integral part of the response observed.

Especially because in vitro administration of MEL can phase shift the firing rate of SCN neurons in brain slices (rat, mouse),[69,144] it is generally believed that MEL mediates these effects through the high-affinity MEL receptors located within the SCN.[29,107,125] This view is supported by the high correlation between the density of MEL receptors within the SCN and the ability of daily MEL administration to entrain the free-running activity rhythm in mammals. Contrary to the rat, mouse, and Djungarian hamster, rodents that can be entrained by daily MEL administrations and in which a high density of MEL receptors is observed within the SCN, the mink (*Mustela vison*) does not appear to have specific MEL receptors (at least 2-iodomelatonin binding sites) within the SCN. This animal does not entrain to MEL.[89] Newborn Syrian hamsters express MEL receptors in the SCN, but shortly after birth the receptor number decreases.[145,146] Young hamsters are entrainable by daily acute MEL administration, while in the adult MEL cannot entrain[129,147,148] or can only do so under particular experimental conditions (eg, long-term infusions).[132,149] Since SCN-lesioned hamsters whose rhythmicity has been restored with fetal hypothalamic graft are entrained by daily MEL injection, and since MEL is known to accelerate the reentrainment of circadian rhythm in rat subjected to a shift in the LD cycle,[134] it is clear that the chronobiotic effect of MEL is the consequence of a direct action on the clock. This conclusion is

supported by the observations that a MEL receptor antagonist (S 22153) in vivo blocks the phase-advancing effect of MEL[83] and that after administration of various MEL receptor agonists (AH-001, AH-017, and GG-012, see *Table I*) an increase in the amplitude of the nocturnal MEL peak is observed.[76]

Which receptor subtypes are involved? Siberian hamsters lacking a functional MT_2 receptor show circadian responses to MEL.[150] Similarly, the most robust entraining response to MEL, synchronization of developing circadian pacemakers in Syrian hamsters by MEL injections,[151] occurs in the absence of a functional MT_2 receptor within the SCN. This strongly suggests the implication of MT_1 receptors or at least a partial redundancy of function between MT_1 and MT_2. In the in vitro experiments in animal models with both subtypes, where effects are obtained with physiological doses of MEL, the mechanisms involved appear to be complex. For example, two distinct effects of MEL have been described: an acute inhibitory effect on neuronal firing and a phase-shifting effect in the rhythm in electrical activity.[55] Until recently, it was assumed that the inhibition of electrical activity was part of the cellular mechanism underlying the phase shifting effect of MEL. However, in mice with a targeted deletion of the MT_1 receptor, the acute inhibitory effect of MEL was abolished, while the phase-shifting effect remained intact.[55] This phase-shift disappears when the MT_2 antagonist 4P-PDOT is added.[32] This suggests that either a low density of MT_2 receptors can still produce phase shift[75] or that an as yet unidentified MEL receptor subtype is involved (see above). In contrast to previous studies, van den Top et al[152] have recently demonstrated the absence of a particular window of sensitivity for MEL to inhibit SCN neuronal activity. Such inhibition is also obtained with the MEL agonist and selective 5-HT_{2c} antagonist S 20098[91] and is blocked with low doses of the MEL antagonist S 20928. Such a lack of a window of sensitivity is in contrast to MEL's phase-shifting effect, and indicates that distinct cellular mechanisms are involved in the acute inhibitory effect and in the phase-shifting effect of MEL. This may be related to the two types of effects observed in vivo after the daily 8- or 16-h MEL infusions[133] described above.

Even though the presence of MT_1 and/or MT_2 receptors appears to be a necessary condition for the chronobiotic effect of MEL, if these high-affinity receptors were the only mechanism involved, then it would be difficult to explain why a high dose of MEL is needed to obtain such an effect in vivo. This suggests that other neural mechanisms are involved. At concentrations as high as those needed to observe an effect on circadian activities in mammals, MEL is known to inhibit 5-HT reuptake in nerve endings.[153,154] A possible interaction between MEL and the 5-HT system within the SCN should thus be considered.

The inhibition of 5-HT reuptake is not crucial for the MEL effect on the circadian rhythms.[155] MEL might then act at the level of the postsynaptic 5-HT receptors. This idea is supported by the observation that administration of 5-HT receptor agonists in vivo also phase shift the rodent circadian clock and by the work of Dugovic et al,[156] who have shown that in vivo exogenous MEL counteracts the 5-HT_{2A} agonist– or antagonist–induced effects on sleep. Eison et al[157] also demonstrated a modulation of 5-HT_{2A} receptor–mediated behavioral responses by exogenous MEL (high dose) and Ying et al[91] found that high dose of MEL exerted inhibitory effect on firing rate in the intergeniculate leaflet by mimicking the effect of 5-HT agonists. Such direct implication of the 5-HT system in the chronobiotic effect of MEL, however, remains to be experimentally demonstrated.

Conclusions and future prospects

Disturbed circadian rhythmicity due to life conditions (shift work, jet lag) or to involuntary circumstances (illness, aging) has been associated with numerous mental and physical disorders. This has important consequences on human safety, performance, and productivity. The importance of circadian (and seasonal) rhythmicity for human health and welfare is becoming increasingly recognized and a need for treatment is now clear.

Problems may occur at various levels in the circadian organization and drugs to reverse theses changes may be directed toward the input pathways, the clock itself, the output pathways, or ultimately the organ expressing a particular rhythm.

Nocturnal secretion of MEL is an output signal of the circadian clock that distributes the circadian message to any structures/organs possessing MEL receptors, within the brain or in the periphery. This explains why MEL appears to act in so many different systems. Moreover, due to the presence of MEL receptors within the SCN itself, when MEL administered exogenously has clear chronobiotic effects. Thus, through an action on the clock, the hormone influences the temporal organization

of a large number of functions (cardiovascular, digestive, immune, etc). This also explains the wide range of reported MEL effects. MEL is thus an attractive candidate for manipulating circadian rhythms in humans.

The assessment of therapeutic potential of MEL calls for a precise delineation of its sites and mechanisms of actions. The recent (and future) development of specific agonists and antagonists for the human MEL receptor subtypes opens new prospects. Without any doubt these drugs are leading to therapeutic applications in dissociating the different MEL actions at the different levels of organization of the system. ❑

Melatonina

La melatonina (MEL) es una hormona que es sintetizada y secretada por la glándula pineal, la cual se ubica en la profundidad del cerebro, en respuesta a señales fotoperiódicas que se transmiten desde la retina a través de un oscilador circadiano que está en el núcleo supraquiasmático del hipotálamo. El ritmo circadiano de la producción y liberación de melatonina, que se caracteriza por una actividad nocturna y un reposo diurno, constituye una importante señal temporal para las estructuras del cuerpo que pueden leerla. La melatonina actúa a través de receptores de alta afinidad que se ubican a nivel central y en numerosos órganos periféricos. Se han clonado y caracterizado diferentes subtipos de receptores: MT_1 y MT_2 (receptores transmembranosos acoplados a proteína-G) y MT_3. Aun cuando su papel fisiológico no está aclarado, las aplicaciones en el manejo del ganado por ahora incluyen el control de la reproducción estacional y la producción de leche. Como potenciales aplicaciones terapéuticas la melatonina exógena o un agonista de melatonina y agonista selectivo del receptor 5-hidroxitryptamina ($5\text{-}HT_{2c}$), como el S 20098, se pueden utilizar para manipular los procesos circadianos como el ciclo sueño vigilia, el cual frecuentemente se desorganiza en muchas condiciones, en especial en el trastorno afectivo estacional.

Mélatonine

La mélatonine (MEL) est une hormone synthétisée et sécrétée par l'épiphyse, glande située profondément dans le cerveau, en réponse à des signaux photopériodiques transmis à partir de la rétine par un oscillateur circadien endogène dans le noyau suprachiasmatique de l'hypothalamus. Le rythme circadien de la production et de la libération de mélatonine, caractérisé par une activité nocturne et une quiescence diurne, est un important signal temporel pour les structures corporelles capables de le lire. La mélatonine agit par l'intermédiaire de récepteurs à haute affinité, tant centraux que présents dans de nombreux organes périphériques. Différents sous-types de récepteurs ont été clonés et caractérisés : MT_1 et MT_2 (récepteurs transmembranaires couplés à la protéine G) et MT_3. Cependant, leur rôle physiologique reste non élucidé, bien que des applications de gestion du cheptel soient déjà utilisées pour contrôler la reproduction saisonnière et la production de lait. Dans les applications thérapeutiques potentielles, la mélatonine exogène ou par exemple, le S 20098, agoniste de la melatonine et antagoniste sélectif du récepteur de la 5-hydroxytryptamine ($5\text{-}HT_{2c}$), peuvent être utilisés pour modifier certains processus circadiens comme le cycle veille-sommeil, qui sont souvent déréglés dans de nombreuses circonstances, tout particulièrement dans les troubles affectifs saisonniers.

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