

Bipolar Disorders and Seasonality

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Abstract

Bipolar disorder (BD) is a severe and common neurodevelopmental psychiatric illness (1 to 4% of the general population). The severity and prognosis of this disease is partly linked to a high rate of recurrence of mood episodes with 70 to 80% relapses on average 2 years after a major episode (depressive or manic), despite treatments. These recurrences may follow a seasonal cyclicity for a significant number of patients. Almost all functions of the body are subject to the circadian rhythm, that is to say a 24-hour cycle. Thus, disorders of this rhythm can have consequences on sleep as well as on metabolism, the functioning of the cardiovascular system, the immune system as well as mood. However, the study of the effect of seasons in BD, presents a complex and heterogeneous literature, which to date does not benefit from an exhaustive synthesis. However, this article tends to improve knowledge of the influence of the biological clock on the symptoms of BD.

Keywords: Bipolar disorder, Circadian rhythms, Depression, Mania, Melatonin, Photoperiod, Pineal gland, Seasonal rhythms, Solar insolation, Suprachiasmatic nucleus

Introduction

Bipolar disorders (BD) are severe psychiatric disorders, of multifactorial origin and with very heterogeneous clinical presentations [1]. This disease begins at an early age with the onset of disorders before the age of 21 for half of affected subjects [2] and presents high morbidity and mortality (WHO), causing poor quality of life with a functional impact [3,4]. These disorders affect 1 to 7% of the world population [5] and are characterized by the recurrence of so-called "manic" mood episodes (defined by an elevation of mood and energy, psychomotor agitation, and a disorder of sleep) or "depressive" (defined by sad mood, reduced energy, psychomotor slowing, and disorder of instinctive behavior).

Seasonal mood changes are well documented in bipolar patients [6]. They are particularly visible in fall and spring. Around the world, psychiatrists have noted that there are seasonal variations in the number of suicides, with increases in the spring [7]. The exact causes of these changes are not known. Many scientists believe that these changes in mood, energy, and behavior are linked to changes in exposure to daylight [8]. Different seasons are associated with different amounts of sunlight during the day and variations in sun

exposure from day to day. Sunlight can trigger changes in our body clock. We have natural circadian or daily rhythms that govern our energy and activation. Some of these rhythms can be activated or changed when we are exposed to sunlight.

Concept of Seasonality

The influence of light and the seasons on mood or instinctive behavior is known by a large part of the population to a more or less marked degree. The influence of the seasons on mood, or on at least one aspect of behavior (for example diet, sleep, activities, etc.), would in fact concern a large part of the general population [9].

In medicine, the history of the concept of seasonality is not recent and appears from the first medical descriptions: this seasonal cyclicity of mood was mentioned in antiquity by Greek doctors. Hippocrates was the first to report the importance of the seasons on mood changes. He believed that "Whoever wishes to study medicine seriously must first observe the development of the seasons." We can also cite Aretaeus of Cappadocia who wrote: "the lethargic must be exposed to the rays of the sun, because their illness is due to darkness".

Specific links between the seasons and psychiatry appeared from the 19th century. In 1825, Esquirol described the case of a patient in remission from depression by three vacations in Italy in autumn-winter during 3 consecutive years [10]. Kraepelin, in 1913, estimated that 4 to 5% of patients suffering from manic-depressive psychosis have a seasonal periodicity, of the autumn type, of their depressive episodes, and of the spring type, of their hypomanic episodes: "depression appears from the autumn and disappears in spring, giving way to a state of excitement" [11]. After Kraepelin, many psychiatrists reported an association between the seasons and the incidence of depressive episodes and manic episodes (such as Lewy and colleagues who published in 1980 the case of a patient with BD, regularly depressed in winter. Lewy subsequently demonstrated the suppression of melatonin secretion by intense light in humans and was thus the first doctor to hypothesize that depression in winter would be linked to a pathologically late secretion of melatonin [12]. These first observations led Rosenthal in 1984 to describe the notion of seasonal depression (designated by the English acronym SAD for Seasonal Affective Disorder) and to make his first trials of phototherapy. Rosenthal then proposed seasonal depression to the National Institute of Mental Health (NIMH) for recognition as a nosographic entity of manic in summer, which responded spectacularly to treatment with phototherapy [13]. On the other hand, patients with depression prioritize processing of negative information over positive input. While there is evidence that emotional bias exists in seasonal affective disorder (SAD) during winter, it is unclear whether such altered cognition exists also during summer [14].

Neuroanatomical Substrate and Molecular and Electrophysiological Basis of the Biological Clock

In vertebrates in regions ranging from tropical to polar zones, the photoperiod is a powerful synchronizer of seasonal changes in the endocrine, immuno-inflammatory, metabolic, and mood systems [15]. This seasonal photoperiodism, as well as the circadian day/night alternation, results in an adaptation of the internal biological clock involving its two main actors which are the supra-chiasmatic nuclei (SCN), and the melatonin secreted by the pineal gland [16]. The peripheral clocks which are dependent on the NSC play an essential role in the synchronization of biological rhythms with this photoperiodism and the day/night alternation.

The central clock, located in the SCN, synchronizes circadian and seasonal rhythms. It is the main pacemaker of biological rhythms and is made up precisely of a network of 20,000 neurons located in the NSC, at the base of the anterior hypothalamus above the optic chiasm [17]. The SCNs are the first structures in the brain to perceive light information coming from the retina from the retino hypothalamic tract. NSCs then encode photic and photoperiodic information

on both a molecular and electrophysiological level. This adaptation to the photoperiod is enabled by changes in the expression of clock genes, and of several neurotransmitters responsible for modifications in the electrical activity of its neurons according to circadian and seasonal rhythms [18].

The main clock genes

The primary molecular mechanisms underlying the generation of core clock rhythms in NSCs include a complex network of feedback loops of interdependent activating and inhibitory transcription-translation reactions that result in the rhythmic expression of major NSC genes [19].

In humans, the two main springs, are genes called *Per* and *Cry*. However, these can only be active if a specific region of their DNA sequences (called "E-box element") receives a visit from two proteins. These two proteins linked to each other (also said to form a complex) are the *CLOCK* protein and the *BMAL1* protein. Their attachment to the "E-box element" of the *Per* and *Cry* genes therefore allows the transcription into messenger RNA (or mRNA) of these genes. Unlike the DNA of genes, mRNA can exit the nucleus through nuclear pores and travel to the cytoplasm where it will be translated into protein by ribosome [20].

The *PER* protein, the result of the translation of the mRNA of the *Per* gene, is rapidly degraded unless it also forms a complex. This complex can consist of *PER* proteins, or of *PER* proteins and *CRY* proteins. These complexes will then penetrate the nucleus of the cell and interact with the *CLOCK*/*BMAL1* complexes so as to render them inactive. This is how the negative feedback loop is created, the *PER* and *CRY* proteins produce genes of the same name, inhibiting their own production [21].

After a certain time, the *PER* and *CRY* protein complexes degrade and are replaced by other complexes that have penetrated the nucleus. But eventually, there will no longer be enough complexes available to block the activation of the *Per* and *Cry* genes because there are no longer any *PER* and *CRY* proteins produced. The inhibition on *CLOCK* / *BMAL1* will then be lifted, and transcription of *Per* and *Cry* mRNAs will resume. Approximately 24 hours will then have passed since the start of the process [22].

Training of the biological clock by photoperiod and day/night cycles

Entrainment corresponds to the stable relationship by which the endogenous period adjusts to the period of the environment. This phenomenon of training the biological clock to time givers is achieved thanks to the synchronization of the NSC to photic and non-photic timers (such as eating rhythm, locomotor activity, outside temperature, melatonin) [23]. Through this training phenomenon, the NSCs produce an

output signal making it possible to orchestrate all biological rhythms and adapt to changes in the environment, particularly seasonal ones. Light signals are important time givers because they allow the body to transmit to the body, thanks to the NSC, not only information on the daily alternation of light and darkness due to the rotation of the earth, but also photoperiodic information., due to the revolution of the earth around the sun, thanks in part to a modulation of the rhythmic expression of clock genes [24]. The NSCs in fact receive, via the retino-hypothalamic tract, a retinal input signal coming from the cells of the ganglionic layer which contain a photopigment called melanopsin and which are depolarized by light. From this light signal, the expression of clock genes will be regulated at the NSC level [25]. Thus, photoperiod modifies the expression of clock genes in E-box-containing NSCs (PER1, PER2, CRY1, Rev-erb α), whereas BMAL1 and CRY2 are not affected. Likewise, daily day/night alternation induces conformational changes in the CRY protein, the expression of certain circadian genes (PER, DEC1) and chromatin remodeling. This input signal modulates the rhythmic expression of clock genes at the NSC level. This rhythmic information is relayed to other parts of the brain, including the pineal gland which will rhythmically secrete melatonin by activation of AA-NAT transcription, but also to peripheral oscillators via the autonomic nervous system. Other mechanisms involved in synchronization with photoperiod NSCs have a central role in the generation of biological rhythms and the molecular mechanisms underlying these generations of rhythms are based on feedback loops that regulate the transcription of genes of the clock [26]. The NSC, by detecting and encoding photic information, will perceive and encode changes in day length (photoperiod) and cause seasonal changes in the downstream pathways and structures (pineal gland, peripheral oscillators) in order to adapt to the seasons. In addition to rhythmic modulation of clock gene expression, there is neuronal plasticity of NSCs that allows adaptation to biological rhythms. In NSCs, these photoperiod adaptation mechanisms include changes in the expression of neurotransmitters and clock genes, which result in changes in rhythmic electrical activity [27]. All of these adaptations to biological rhythms in the NSC will be responsible for changes in other structures of the brain, including the pineal gland which plays a major role in the regulation of seasonal cycles by secreting melatonin as we will see later. At the electro-physiological level, the detection of light radiation is one of the main functions of NSC through their ability to detect changes in ambient lighting level during the day/night cycle. The ability of the NSC to detect changes in irradiance is a prerequisite for determining day length and therefore changes in photoperiod. The NSCs are thus in phase with progressive changes in day length. The responses of neurons to variations in light intensity and therefore day length results in a variation in the number and profile of electrically activated neurons. The response of neurons to light is predominantly centered around the light intensities that occur at dawn and dusk. This response range of neurons is relatively narrow compared

to the range of light intensities that actually occur in the environment. The neurons transmit the "day/night" signal. NSCs can only weakly discriminate light intensities that occur throughout the day (e.g. they fail to discriminate whether the day is sunny or cloudy) [26]. It is thus the variation in number and electrical activity profile of the cells in the NSC which makes it possible to differentiate between short and long photoperiods. The combined electrical activity of neurons produces electrical oscillations resulting in a rhythmic output signal [28].

At the molecular level, in addition to variations in the expression of clock genes induced by light, several neurotransmitters are involved in the synchronization of neurons in NSC and play a key role in the "seasonal" coding of NSC. Vasoactive intestinal peptide (VIP) in ventral SCN neurons allows synchronization of clock neurons. Its absence attenuates electrical activity and thus molecular rhythmicity. In mice, the absence of VIP or its receptor causes the loss of circadian rhythms and an inability to adapt to the light/dark cycle [29]. The importance of VIP in seasonal adaptation has been highlighted. In Knock-out (KO) mice for VIP which showed no difference in electrical activity between long and short photoperiods and which were unable to encode periodic information. Concerning Arginine-Vasopressin (AVP), its rhythmic expression is driven by intrinsic molecular feedback loops of the central circadian clock. Its expression rhythm is subject to photoperiodic changes with a higher peak of expression in long than short photoperiods [30]. Furthermore, AVP has been shown *in vitro* to restore NSC rhythmicity and synchrony in VIP-deficient mice. The photoperiod also affects the GABAergic inhibition-excitation balance. GABA is the most prevalent neurotransmitter in SCNs. In mice, in a long photoperiod, the neurons are mainly excitatory, in a short photoperiod the neurons are more inhibitory [31]. The photoperiod also modifies the balance of dopamine and somatostatin. This underlines the important influence of the photoperiod on neurotransmission [32]. These data demonstrate the ability of NSCs to adapt to seasonal rhythms thanks to neuronal plasticity of NSCs both at an electrical and molecular level in response to the photoperiod. These two levels, molecular and electro-physiological, lead to a set of changes in the downstream pathways and structures (pineal gland, peripheral oscillators) in order to adapt to the seasons.

Effect on Bipolar Symptoms

Sunlight hits special cells in the retina of our eyes, and these cells transmit information to the suprachiasmatic nucleus (SCN) in our hypothalamus. When the SCN is activated, it triggers changes in the secretions of hormones that regulate metabolism. These changes also affect the release of certain neurotransmitters (e.g., serotonin) that influence mood, sleep, and behavior. Seasonal mood swings are more difficult for people with BD, so they have variations in CLOCK genes,

which govern circadian rhythms. These variations increase the effects of seasonal changes in sunlight on mood, energy and behaviors [33].

Furthermore, seasonal effects vary with latitude, more strongly in the northern hemisphere than in the southern hemisphere. Indeed, these latitudinal differences in fluctuation are the result of the photosynthetic activity of plants. Seasonal variations in CO₂ are therefore more pronounced in the northern hemisphere, where seasonal temperature variations lead to very large differences in summer plant photosynthesis in winter. Consequently, the length of the photoperiod has a primordial role in modifying mood: its variation during the different seasons leads humans and animals to an adaptation of the biorhythm. The photoperiod reaches its maximum extension in summer and its minimum in winter. This environmental model reveals biological and clinical implications for humans, since the light stimulus is received by the retina and transformed into an electrical signal that interacts with the suprachiasmatic nucleus of the hypothalamus (SCN), known as the main endogenous pacemaker. The SCN regulates the activity of many organs, mainly the pineal gland, in order to modify biorhythms to better adapt to seasonal variations. Bipolar individuals have circadian genetic mutations that compromise normal synchronization with environmental stimuli, such as sunlight. It was observed that mice carrying a mutation in one of the main circadian rhythm genes, the CLOCK gene, had a behavioral profile strikingly similar to that of people who experience a mania episode of BD [34].

Melatonin secretion interacts with transcription of the CLOCK gene in the pituitary gland to modulate hypothalamic hormone production. Thus, a disrupted interaction between the central nervous system and the rest of the body can have repercussions at all levels [35]:

- Metabolic disturbances.
- Circadian disruptions and the sleep-wake rhythm (due to a dysfunction of the hypothalamus-pituitary-adrenal axis).
- An altered and compromised immune response.
- Increased oxidative stress at the cellular level.

Bipolar Clock and BD

Lewy is one of the first authors to hypothesize that patients with BD present disturbances in their biological rhythms. Indeed, in 1985, he hypothesized that the process of suppressing melatonin secretion by light would be altered in patients with BD. More specifically, it suggests that patients with BD have a suppression of melatonin secretion at lower brightness than subjects without BD [36]. In his study carried out in 4 patients with BD and 6 healthy volunteers, he found

that in patients with TB exposure to fluorescence of 500 lux at 2 a.m. led to a 50% reduction in melatonin secretion while this exposure had no effect in control subjects [37]. Fluorescence at 1500 lux completely reduces melatonin secretion in patients at concentrations observed during the day, i.e. less than 10 pg/ml. On the other hand, in control subjects, a reduction in melatonin of 60% is observed at this same intensity. The author thus concludes that there is hypersensitivity in the secretion of melatonin in response to light. This increase in reactivity to light could explain an increase in vulnerability to seasonal changes in patients with TB. This hypersensitivity to external stimuli is often reported in patients with BD (wearing sunglasses inside the house) and the experiment carried out by Lewy was confirmed by a visual evoked potential technique [32]. Moreover, numerous disturbances in biological rhythms have been associated with BD both during mood episodes and during periods of remission. The circadian markers mainly studied in BD are sleep-wake rhythms, the rhythms of hormonal secretions of melatonin (plasma, urinary, salivary) and cortisol (plasma or salivary) and the circadian rhythm of body temperature. These endogenous rhythms are defined by different circadian markers including the phase, period and amplitude of these rhythms [38].

The sleep/wake rhythm represents one of the main markers of circadian rhythms. It is measured by different techniques such as sleep diaries, typical chrono questionnaires and actigraphy. These different techniques made it possible to emphasize circadian variations in morningness-eveningness, amplitude and stability in BD [39]. Indeed, patients with BD compared to control subjects present a circadian phase preference for the evening [40,41], a less good amplitude of their circadian rhythm with a sensitivity to the reduction of sleep (with a more lethargic state following reduced sleep or languid) and less stability of their circadian rhythm with difficulty adapting to changes in rhythms (rigid). Indeed, in a study comparing patients with BD in remission and healthy controls, confirms previous studies which show that patients with BD are more inclined to an evening chronotype thanks to using a phase preference questionnaire (the Composite Scale of Morningness CSM), and have a more languid and more rigid circadian typology assessed using a questionnaire the Circadian Type Inventory CTI [42]. This questionnaire assesses the dimensions of stability of rhythms (flexibility/rigidity) and amplitude of rhythms (languor/vigor). Furthermore, abnormalities in sleep-wake cycles have also been highlighted using actigraphy, which is an ecological and objective measurement tool for sleep/wake activity. Thus, a recent meta-analysis involving 9 studies comparing the sleep actigraphic parameters of 202 patients with BD in remission compared to 210 healthy control subjects shows persistent abnormalities: longer sleep duration, longer sleep onset latency, poorer sleep efficiency, waking up after first falling asleep more frequently in patients with BD compared to controls [32]. These data are taken in account in a more

recent review of literature [43]. Furthermore, other studies, in addition to abnormalities in basic sleep parameters (higher sleep fragmentation index, etc.) highlight greater variability in actigraphic parameters in patients with BD, reflecting greater instability of circadian rhythms [44]. In fact, these studies show poorer inter-daily stability, and variability in bedtime, wake-up time or in the duration and efficiency of sleep [45].

Effect on Bipolar Behaviors

Changes in mood and energy can change information processing strategies (the ability to evaluate and consider information). These subtle changes in personality or behavior can be understood biologically, they are more marked in bipolar people [46].

Tending towards a hypomanic or manic state disrupts the response to neurotransmitters. Interconnections between brain regions can also be dysregulated. For example, there may be changes in dopamine pathways that contribute to the experience of pleasure and motivation. As a result, we may continue to experience positive emotions and feel motivated to seek out more pleasant experiences [46,47]. The bipolar patient knows intellectually that he is taking risks, because he will not be able to regulate his behavior. He will not feel the risks, he will be less likely to experience or integrate negative emotions which could help him perceive the consequences and thus modulate his behavior [48]. For example, in hypomania, it will be less sensitive to anxiety. And sometimes, anxiety can serve as a warning sign, helping us to think about the consequences of our actions. There is a thin space between anxiety, alertness and concentration. Sudden changes in mood can reactivate negative patterns of thoughts, memories and attitudes [49]. The patient feels like he is falling back into his ruts by returning to his negative thoughts, leading him to rumination.

To cope with seasonal changes, one needs to have a long-term overview of one's illness, its trends and its effects. The most effective method is to take a look at your past calendars to check the accuracy in predicting seasonal effects. Note all the changes in activity implemented and which were effective in order to be able to draw inspiration from them in the years to come [50].

Exogenous melatonin exerts a therapeutic effect in bipolar patients by normalizing the sleep/wake cycle and can improve both sleep duration and quality. Additionally, recent research has shown that exogenous melatonin may have a marked improvement in affective symptoms. However, one risk of prescribing melatonin is inducing a manic episode [32].

Limitations

The extent of knowledge in the field covered in this article is constantly evolving, the data presented and analyzed can

quickly become obsolete. The relevant articles cited reflect the most recent research.

Conclusion

There is no specific abnormality of circadian rhythms and sleep associated with seasonal rhythm disorders in patients with BD. Indeed, there are no circadian trait markers associated with the seasonal characteristic of mood episodes based on subjective (questionnaires) and objective (actigraphy) measurements. Patients with mood episodes of bipolar patients sensitive to seasonality seem to be treated more with lithium combined with atypical antipsychotics, which opens avenues for reflection on the effect of these molecules on vulnerability to the effect of the seasons. In fact, lithium stabilizes circadian rhythms. Lithium could thus be the molecule of first choice in the treatment of patients sensitive to seasonality through its effect on the biological clock; lithium could also play on the synchronization of seasonal rhythms. Furthermore, atypical antipsychotics could also be treatments of choice in patients sensitive to the seasons. Atypical antipsychotics would not act directly on seasonality by passing on circadian voices, but their effect could be through their action on the monoaminergic pathways which allow the synchronization of rhythms through their effect on the central clock.

Avenues for research into other markers of seasonality in BD with the study of plasma melatonin (central hormone of seasonality as we have seen), the search for genetic or epigenetic variants of the genes of the synthesis pathway of melatonin, and in neuroimaging via the search for serotonergic brain markers linked to seasonality. The most important data in BDs are phase delay in melatonin secretion, seasonal fluctuations in melatonin secretion higher than in normal control, high SERT binding than in normal control, reduced carrier availability dopamine.

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