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Chapter

Neuroprotection, Photoperiod, and Sleep

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Abstract

After an acquired brain injury, responses that induce cell death are activated; however, neuroprotective mechanisms are also activated. The relation between these responses determines the destination of the damaged tissue. This relation presents variations throughout the day; numerous studies have shown that the onset of a stroke occurs preferably in the morning. In the rat, ischemia causes more damage when it is induced during the night. The damage caused by a traumatic brain injury (TBI), in the rat, varies depending on the time of day it is induced. Minor behavioral damage has been reported when the TBI occurs during the night, a period that coincides with the wakefulness of the rat. It also has been observed that sleep deprivation accelerates the recovery. Our group has documented that this is due, in part, to a difference in the degree of activation of cannabinergic, GABAergyc, and glutamatergic systems.

Keywords: circadian rhythm, sleep deprivation, traumatic brain injury, stroke, cannabinergic system, glutamatergic system, GABAergyc system

1. Introduction

Recent research on acquired brain injury, the pathophysiological processes involved, as well as the mechanisms of morphological and functional recovery, have led, among other essential aspects, to the concept of neuroprotection [1]. This term refers to the use of any therapeutic modality that prevents or delays cell death resulting from a neuronal injury. In this sense, neuroprotection could be considered as a cytoprotection technique similar to cardioprotection or vasoprotection [2, 3].

Also, the term neuroprotection has been used to refer to self-protective responses that the body displays when it undergoes an acquired brain injury and tries to maintain the integrity and functionality of the brain [4]. The management of the term neuroprotection, in this sense, is more recent and emphasizes the balance of the body's responses to an event of ischemia and/or traumatic brain injury (TBI).

In a TBI, two types of lesions can be identified. The primary lesion, which corresponds to mechanical damage to the parenchyma or the vasculature, occurs

at the moment of impact and is not reversible or curable and the secondary lesion, which corresponds to late effects, which occur hours to days post-trauma, involves a series of functional, structural, cellular, and molecular changes that cause neuronal damage. Among the events that occur, ischemia has been described. When the flow of blood to the brain tissue ceases, the entry of oxygen and nutrients and the exit of potentially toxic metabolites are severely damaged, resulting in biochemical changes in the affected brain area. There is a depletion of glucose and glycogen and failure of Na/K ATPase and other pumps, which result in a decrease in excitation threshold, presence of action potentials, release of excitatory neurotransmitters such as glutamate, massive entry of calcium, and activation of proteases, lipases, and nucleases, among other enzymes [5]. However, as mentioned earlier, neuroprotective responses are also induced; for example, the GABAergic and cannabinergic systems are activated [6, 7]. The balance between both responses will determine the outcome of the damaged tissue [4].

Indeed, the release of glutamate and the activation of its ionotropic receptors are the main events that result in cell death as a consequence of a TBI or cerebral ischemic attack with acute hypoxia [8–10]. The increase in GABAergic synaptic transmission may have neuroprotective effects against cerebral ischemia, and its inhibition increases the alterations induced by this event, while the inhibition of excitatory signals or excitatory neurotransmitters results in the cytoprotection of ischemic brain tissue [6, 11]. GABA mimetic drugs have a protective effect. Thus, administration of GABAA agonists such as benzodiazepines or muscimol attenuates the damage produced by a TBI [12, 13], while bicuculline, a GABAA antagonist, increases it [12].

In vitro and *in vivo* data suggest that the cannabinergic system is a component of mammalian neuroprotective mechanisms that an organism displays after suffering an insult such as a TBI [7, 14–17]. Endocannabinoid anandamide and 2-arachidonoylglycerol (2-Ag) increase after an acquired brain injury [14, 15] and serve as signaling mediators in integrating inhibitory and excitatory synaptic transmission, as they could regulate glutamate and GABA release [17]. Besides, recently it has been reported that 2-Ag keeps brain homeostasis by exerting anti-inflammatory effects in response to harmful insults [17].

2. Neuroprotection and photoperiod

The cerebral ischemic attack, similar to the heart attack, has a marked diurnal rhythm. Numerous studies have shown that the time of onset of cerebral vascular accidents, as well as transient ischemic attacks, occurs preferably between 6:00 and 12:00 h in the morning that is, after the subject gets up and begins to present activity [18–20]. Numerous variables have been mentioned as responsible for this circadian pattern, among which are postural changes, circadian variations of platelet aggregation, thrombolysis, blood pressure, cardiac rhythm, and circulating concentrations of catecholamines, whose maximum levels occur just in this period. In the rat, ischemia causes more significant damage if it is induced in the hours of darkness compared to the hours of light [21].

Our group has analyzed the severity of a TBI concerning the photoperiod. Using the rat as a model, we have found that the recovery from a TBI induced by the technique of "closed head injury" presents diurnal variations, recovery being better if the trauma occurs in the hours of darkness concerning daylight hours [22–24]. In other words, there seems to be a greater neuroprotection response in the hours of darkness. The fact that the functionality of the brain is not the same in the hours of light as in the hours of darkness is not surprising; many pieces of

evidence indicate the importance of rhythms in general, and in particular of the circadian rhythms in physiology. The presence of circadian rhythms has been explained as an adaptive response of the different organisms to the environmental variables. All species from cyanobacteria to humans have these rhythms that serve to anticipate the daily variations of different variables such as temperature, light, or food intake. It is accepted that virtually any physiological parameter that has been measured for a period of 24 h in humans has fluctuations [25, 26]. Several aspects of brain physiology, neuronal activity, and secretion of neurotransmitters, among others, change throughout the day, in such a way that the cerebral functions present circadian variations, dependent on the time of day, although it should be noted that they also depend on the sleep-wake cycle [27, 28]. Circadian rhythms in mammals are generated by the suprachiasmatic nucleus (SCN) of the hypothalamus, and both GABA and glutamate are intimately related to the function of this nucleus. Indeed, the photic information received by the SCN comes directly from the retina through the hypothalamic retinal tract, which releases glutamate, and indirectly through the hypothalamic geniculate tract that releases GABA and neuropeptide Y [29]; besides, GABA is one of the main neurotransmitters present in the SCN.

The variability in neuroprotection associated with the photoperiod can be explained by considering that the endogenous levels of practically any endogenous molecule present variations during the different phases of photoperiod. Diurnal variations have been reported in the circulating levels of heat shock proteins (HSPs) [30], as well as brain-derived neurotrophic factor (BDNF) and its receptors in the prefrontal cortex [31], of anandamide in cerebrospinal fluid, pons, hippocampus, and hypothalamus [32]. Our group found diurnal variations in CB1 cannabinoid receptor expression in the hippocampus [33], pons [34] and cerebral cortex [23].

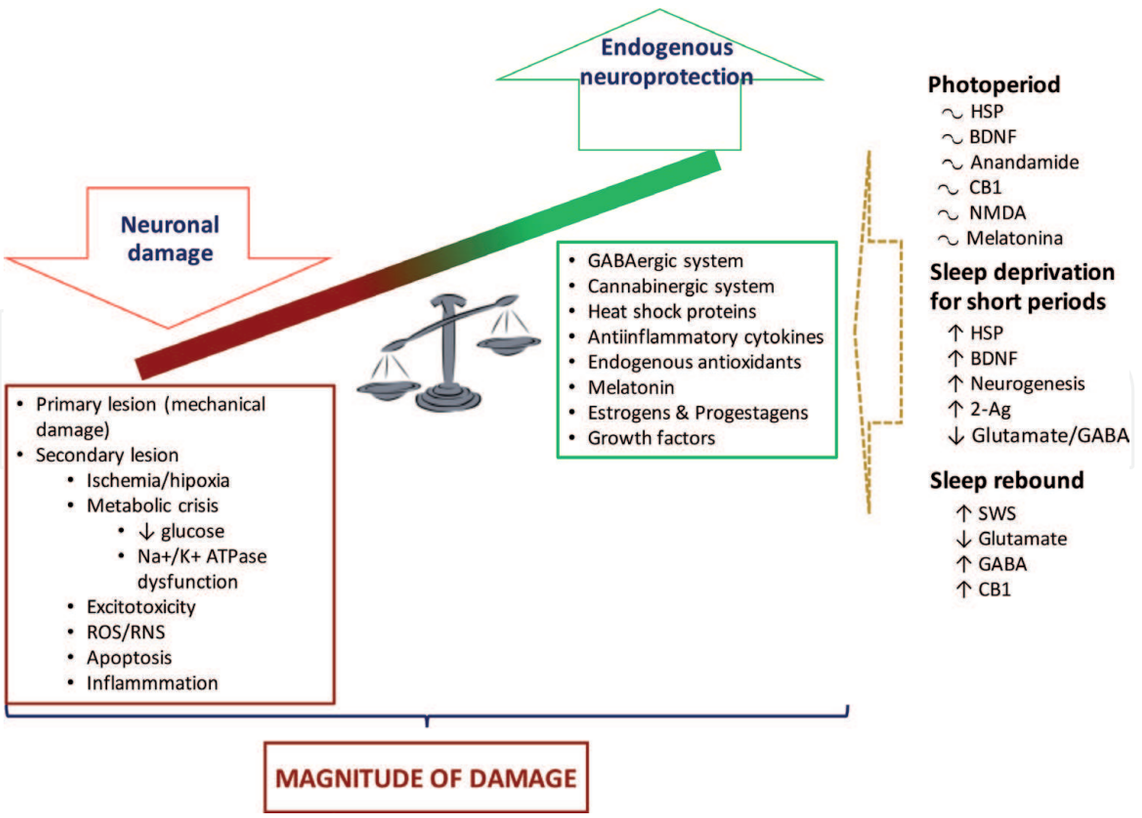

Figure 1.
Mechanisms of neuronal damage, endogenous neuroprotection, and its relationship with photoperiod, sleep deprivation for short periods, and sleep rebound. BDNF: brain-derived neurotrophic factor; CB1: cannabinoid receptor type 1; GABA: gamma-aminobutyric acid; HSP: heat shock proteins; NMDA: N-methyl-D-aspartate receptor; 2-Ag: 2-arachidonoylglycerol; and SWS: slow wave sleep. Data obtained from Refs. [4-7, 23, 24, 31-34, 71-86, 92-95].

Besides, we recently reported diurnal variations in the expression of the NMDA receptor in motor cortex [24] (see **Figure 1**).

On the other hand, it has been reported that the TBI causes circadian dysregulations of blood pressure, heart rate, body temperature [35], hormonal cycles [36], and the sleep-wake cycle [37, 38]. Patients who suffered a severe TBI do not have a perceptible sleep/wake rhythm on the first or second day after the injury, and only half of them will have recovered a consolidated day/night pattern of wakefulness and sleep, 8 days later. The recovery of a circadian organization is a predictive factor of patient wellness [39]. It has been suggested that patients with lesions in the hypothalamus and the SCN will have poor outcomes [40]. Recent data from the literature indicate that even a mild TBI causes damage in hypothalamic structural and functional connectivity [41]. Also, it has been shown that the expression of clock genes such as BMAL1 and Cry1 is disrupted in the SCN and hippocampus of rats that are subjected to TBI [42].

3. Neuroprotection and sleep

Numerous studies have documented sleep-wake disturbances (SWD) in adults post-TBI, with excessive diurnal somnolence and insomnia being the biggest complaints. However, other sleep disorders such as narcolepsy, restless leg syndrome, parasomnias, and obstructive and central sleep apnea have also been reported [39]. Several studies indicate that hypersomnia following TBI has a prevalence varying between 50 and 85% [39, 43]. If the onset of hypersomnolence is from the traumatic event, it is called posttraumatic hypersomnia (PH) and is a hallmark of severe TBI. It has been reported that PH is related to direct injury to the alerting histaminergic tuberomammillary neurons, which are reduced by approximately 40% after severe TBI [44]. Also documented are fatigue and hypersomnia following mild TBI associated with the injury of the lower portion of the ascending reticular activating system between the pontine reticular formation and the intralaminar thalamic nucleus, using diffusion tensor tractography [45].

Botchway et al. [46] reported that even 20 years after a TBI in childhood, young adulthood present increased risk of SWD and that this is more common after a moderate TBI than after a severe one.

Haboubi et al. [47] found that up to 46% of patients reported insomnia that persisted beyond 6 months after mild TBI. Insomnia is reported more frequently with milder forms of TBI injuries [48] and has been associated with head trauma involving lower frontal and anterior temporal regions, including the basal forebrain as it affects the area involved in sleep initiation [39, 49].

Zhou [41], using advanced quantitative magnetic resonance imaging techniques, showed that disruption of functional and structural hypothalamic connectivity in patients with mild TBI was associated with fatigue and sleep problems.

Hypersomnolence has been associated with a decrease in the number of hypocretin-positive cells in experimental TBI models [50–52]. Also, an increased number of awakenings associated with an increase in reactive microglia in thalamic regions have been reported [53].

On the other hand, there are few data in the literature that support the neuroprotective role of sleep or wakefulness. Although, when a child falls and hits his/her head, a general recommendation says: “Do not let him sleep”; there is no reliable data in the literature to support that this sleep deprivation will have some protective effect. More informed recommendations indicate that if the child is sleepy, he/she is allowed to sleep, but that he must be awakened every 2 h to verify that he/she speaks, moves the four extremities and that is oriented [54].

It is worth noting that there is extensive literature that supports that sleep deprivation for prolonged periods impairs many physiological functions and causes death [55–58]. Total sleep deprivation (TSD) in rats causes deterioration in health whose end is death in a period between 11 and 32 days [56], while selectively rapid eye movement sleep deprivation (REMSD) causes death between 16 and 54 days [57].

Nevertheless, recent evidence suggests that sleep deprivation for shorter periods may be neuroprotective. Indeed, several studies in focal and global cerebral ischemia [59, 61, 65–67], cardiac arrest [60] or TBI [64, 68, 69] murine models have documented that both TSD [59, 61, 64–66, 69] and REMSD [60, 64, 67] have neuroprotective effects, whether they are applied before the insult [59–61, 65, 66] or after it [64, 67, 69] as summarized in **Table 1**. However, some studies indicate that sleep deprivation for short periods had no effect [68] or, its effect was deleterious [62, 63] (see **Table 1**).

As can be seen in **Table 1**, in some of the cases, sleep deprivation for short periods of time was applied before the noxious stimulus so it could be considered as a preconditioning stimulus [70], that is, a stimulus that triggers the activation of the endogenous neuroprotection response and prepares the organism against a harmful event of greater wingspan. However, in other studies indicated in **Table 1**, sleep deprivation for short periods was applied after the noxious stimulus, so it would rather act as a neuroprotective factor by delaying and/or decreasing the secondary lesion. In this sense, several reports in the literature suggest that sleep deprivation for short periods increase the expression of neuroprotective molecules like HSP, growth factors, and plasticity-related genes [71–73]. It also has been reported that TSD for short periods produces neurogenesis in the hippocampus [74, 75] (see **Figure 1**).

Another factor that could be participating in the neuroprotective role of sleep deprivation for short periods is the balance between glutamatergic and GABAergic systems, which both sleep deprivation and TBI produce. In the literature, there are reports that TBI increases both glutamate [76–78] and GABA [79]. Also, the expression of GABAA receptors [80, 81] and NMDA [82] is modified; there are also several reports that indicate that sleep deprivation for short periods changes the release of both glutamate and GABA. REMSD increases the level of glutamate [83], as well as that of GABA but reduces the glutamate/GABA ratio [84]. These modifications could be significant in events such as TBI or ischemia since they would be regulating the excitotoxicity produced by glutamate. They could also be correlated with reports showing that sleep deprivation for short periods modifies the expression and/or replacement of NMDA receptors [85, 86]. For example, McDermott [87] shows that the REMSD for 72 h increases the intracellular NMDA levels, which could be interpreted as a down-regulation in response to the increase of glutamate; in the same way, several investigations show that the sleep deprivation for short periods can be an event that prevents the glutamate toxicity mediated by NMDA receptors [88]. As for GABAA receptors, there are reports that sleep deprivation for short periods increases their expression [89, 90], and/or modifies the expression of some subunits, which may explain functional changes in GABAergic transmission [91].

The cannabinergic system could also be participating in the neuroprotective effect of sleep deprivation for short periods. It has been reported that circulating 2-Ag increases with sleep deprivation [92].

Also, it is worth noting that TSD induces a subsequent increase or rebound in slow-wave or high-amplitude electroencephalographic activity during slow wave sleep (SWS) while REMD induces an increase or rebound in REMS [93], so it is possible that the sleep rebound is the neuroprotective factor. This is in agreement with the findings of Brager et al. [94] who utilized remote preconditioning to prevent damage in a focal brain ischemia model. They found that remote preconditioning was associated with an increase of SWS. Also, sleep rebound appears to reduce the cerebral cortex level of glutamate [83] and increase that of GABA [95]. Besides, we

have documented that the rebound after REMSD increases the expression of the CB1 cannabinoid receptors in the rat pons [34], which could have a neuroprotective effect.

Also, during sleep rebound, the function of the glymphatic system is favored and therefore the elimination of toxic brain substances [96–98].

Reference	Damage model	Sleep deprivation (method and schedule)	Main findings	Outcome
Hsu et al. [59]	Global cerebral ischemia in rat	TSD for 5 days before a transient global cerebral ischemia	Attenuation of the damage of pyramidal cells in the hippocampal CA1 and glial reactions	⇑
Weil et al. [60]	Cardiac arrest in mice	48 h of REMSD immediately before cardiac arrest	Improved ischemic outcome. Lesser neuronal hippocampal damage and increased gene expression of IL-6 and IL-10	⇑
Moldovan et al. [61]	Focal cerebral ischemia in rat	6 h of TSD immediately before focal cerebral ischemia	Decreased loss of functions and a smaller infarct volume	⇑
Gao et al. [62]	Focal cerebral ischemia in rat	TSD for 12 h, 12 h after focal cerebral ischemia. TSD for 12 h, for consecutive 3 days 12 h after ischemia	Both sleep deprivation schedules increased the infarct volume and the number of damaged cells	⇓
Zunzunegui et al. [63]	Focal cerebral ischemia in rat	TSD for 12 h, for consecutive 3 days 12 h after ischemia	Lower recovery of forearm motor skills, reduction in axonal sprouting, and synaptophysin expression	⇓
Martinez Vargas et al. [64]	TBI in rat	REMSD and TSD for 24 h immediately after a moderate TBI	Increase in the neurobehavioral recovery and reduction in the histological damage	⇑
Cam et al. [65]	Focal cerebral ischemia in rat	6 h of TSD immediately before focal cerebral ischemia	Reduction in infarct volume associated with an increase in the amount of SWS and REMS.	⇑
Pace et al. [66]	Focal cerebral ischemia in rat	6 h of TSD immediately before focal cerebral ischemia	Reduction in infarct volume associated with a reduction in up-regulation of genes involved in cell cycle regulation and immune response.	⇑
Cheng et al. [67]	Global cerebral ischemia in rat	REMSD for 12 h/day for 3 days 48 h after global cerebral ischemia and reperfusion	Improvement in cognitive function, increased number of BrdU- and BrdU/NSE-positive cells as well as hippocampal BDNF expression	⇑
Caron and Stephenson [68]	TBI in rat	TSD for 48 h or chronic sleep restriction (6 h of sleep/day for 10 days) following mild TBI	TSD or CSR did not exacerbate the neuronal damage induced by TBI	=
Morawska et al. [69]	TBI in rat	Increased sleep with sodium oxybate or TSD (6 h daily/5 d) starting 1 day after TBI	Enhanced encephalographic slow-wave activity. Markedly reduced diffuse axonal damage in the cortex and hippocampus, and improved memory impairment	⇑

SWS, slow wave sleep; REMS, rapid eye movement sleep; TBI, traumatic brain injury; and CSR, Chronic sleep restriction.

Table 1.
REMSD, rapid eye movement sleep deprivation. TSD, total sleep deprivation.

4. Sleep deprivation in humans

The TSD or REMSD data for short periods indicated in the previous section were obtained in animal models, but what is known in humans?

Recent studies indicate that our society is sleeping less and less and that this has a negative impact on health and wellbeing. Between 7 and 8 h/night of sleep is recommended in adults, although this time varies from person to person. Having an insufficient sleep in quantity or quality for multiple nights causes a debt of sleep that cannot be recovered and increases the risk of stroke, obesity, diabetes Mellitus type 2, and cardiovascular disease [99].

However, numerous studies have reported the effectiveness of TSD for one night in patients with depression; the first to report this were Pflug and Tolle, in 1971 [100]. Subsequently, Vogel et al. [101] described that the REMSD was also effective. Gillin [102], in 1983, pointed out that of a total of 852 patients who were TSD or REMSD for one or more nights, 493 (57.9%) were reported to have "improved", but it is recognized that this improvement in mood is transient and it is currently recommended that the TSD or REMSD be combined with sleep phase advance (SPA), pharmacotherapy, and sometimes also phototherapy [103].

Several studies have tried to find the mechanism by which the TSD or REMSD are effective in mood improvement. In this sense, some of the effects of sleep deprivation or the rebound could be considered as neuroprotective; for example, Davies et al. observed that TSD for 24 h increases the serum levels of tryptophan, taurine, and serotonin, which could explain, in part, the antidepressant effect of deprivation [104]. It is worth noting that taurine has been related to cell volume changes triggered by different neurological diseases that produce secondary damage to ischemia [105]. This role is associated with its participation as osmolyte, which has been demonstrated by characterizing the increase in its extracellular concentration and its decrease in the intracellular one. Taurine can regulate the edema induced by the glutamate released during the excitotoxic cascade after a TBI. The nonvesicular release of taurine is an essential protective mechanism to prevent cell lysis, since, upon release to the extracellular environment, there is a change in the direction of mobilization of ions and water [106].

Hefti et al. [107] showed an increased expression of mGluR5 glutamate receptor in the cingulate cortex, insula, medial temporal lobe, parahippocampal gyrus, striatum, and amygdala of healthy men after 33 h of TSD. Previously, some authors had reported that the activation of this receptor decreases the damage, using animal models of cerebral focal ischemia [108] and spinal cord injury [109].

Gorgulu and Caliyurt [110] demonstrated an increase in the concentration of serum BDNF in patients with depression treated with three overnight TSD over a week; nevertheless, in healthy subjects, TSD did not affect the level of BDNF.

In the course of TSD, the concentration of cortisol increases considerably as a result of stimulation of the hypothalamic-pituitary-adrenal axis. The rebound after TSD resulted in a significant reduction of cortisol and increase of growth hormone (GH) secretion driven by the increase of SWS [111]. Recently, neuroprotection has been identified as one of the functions of GH [112, 113].

Also, the level of thyroid hormones increases during sleep deprivation. It is the result of the stimulation of the hypothalamic-pituitary-thyroid axis [114]. It has also been described that thyroid hormones play a neuroprotective role in acute cerebrovascular disorders [115].

However, some studies show effects of TSD that could not be considered as neuroprotective; for example, Trivedi et al. [116] found that glutathione, ATP, cysteine, and homocysteine levels in plasma were significantly reduced as a result of one night of TSD, while Meier-Ewert et al. [117] reported that one night of TSD

increased serum C reactive protein concentrations. Also, one night of TSD causes an increase of serum concentration of interleukin 6 (IL-6), a proinflammatory cytokine in depressive patients as in healthy subjects; but in healthy individuals sleep rebound increased the level of interleukin-1-receptor antagonist (IL-1RA) [118], which inhibits the action of the proinflammatory interleukins 1alpha and 1beta.

Some deleterious effects attributed to the TSD may be influenced by the deprivation method; for example, Gil-Lozano et al. [119] reported that overnight TSD with nocturnal light exposure disrupted the melatonin and cortisol profiles and increased insulin resistance. These alterations were not observed in TSD participants maintained under dark conditions.

5. Limitations

Studies on the impact of acute sleep deprivation and its neuroprotective effects in humans against acquired brain damage are scarce. However, studies performed in subjects without brain injury indicate the existence of neuroprotective mechanisms, as long as it is a TSD for short or acute periods (24 h). In order to propose sleep deprivation as a neuroprotective mechanism and incorporate it as part of the treatment against TBI, more studies are still needed.

6. Perspectives

The importance of the TBI as a public health problem worldwide requires us to understand the pathophysiological changes underlying this neurological event, as well as the processes that favor the activation of endogenous neuroprotection, in order to apply them as a possible therapeutic strategy.

The previous evidence highlights the importance of considering the time of the day when acquired brain injury is established. The alterations found as a consequence of this event are heterogeneous and complex, ranging from molecular changes to behavioral modifications; as pointed before, TBI causes dysregulation of sleep-wake cycle and homeostasis unbalance including many neuropeptide and hormones changes.

In many of the alterations induced by an acquired brain damage, the participation of neurotransmission systems such as GABAergic, glutamatergic, and cannabinergic is fundamental. These, like all endogenous molecules, have a diurnal variation; such variations, in the same way, affect the sleep-wake cycle. Evidence in animal models of the neuroprotective effect of sleep deprivation for short periods encourages us to continue researching this.

Knowing the relationship between neuroprotection, photoperiod, and sleep, as well as the participation of the neurotransmission systems involved in the TBI, opens a window in their study as potential biomarkers or therapeutic targets. With this approach, it will probably benefit a higher number of patients with acquired brain damage.

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