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REVIEW ARTICLE

Zebrafish as a Tool in the Study of Sleep and Memory-related Disorders

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Abstract: Sleep is an evolutionarily conserved phenomenon, being an important biological necessity for the learning process and memory consolidation. The brain displays two types of electrical activity during sleep: slow-wave activity or Non-Rapid Eye Movement (NREM) sleep, and desynchronized brain wave activity or Rapid Eye Movement (REM) sleep. There are many theories regarding "Why we need to sleep?"; one of them is the synaptic homeostasis. This theory suggests the role of sleep in the restoration of synaptic homeostasis, which is destabilized by synaptic strengthening triggered by learning during waking and by synaptogenesis during development. Sleep diminishes the plasticity load on neurons and other cells to normalize synaptic strength whereas it reestablishes neuronal selectivity and the ability to learn, leading to the consolidation and integration of memories. The use of zebrafish as a tool to assess sleep and its disorders is growing, although sleep in this animal is not yet divided, for example, into REM and NREM states. However, zebrafish are known to have a regulated daytime circadian rhythm, and their sleep state is characterized by periods of inactivity accompanied by an increase in arousal threshold, preference for resting place, and the "rebound sleep effect" phenomenon, which causes an increased slow-wave activity after a forced waking period. In addition, drugs known to modulate sleep, such as melatonin, nootropics, and nicotine have been tested in zebrafish. In this review, we discuss the use of zebrafish as a model to investigate sleep mechanisms and their regulation, demonstrating this species as a promising model for sleep research.

Keywords: Zebrafish, sleep, sleep deprivation, memory, learning, neurological disorders.

1. INTRODUCTION

Sleep is an integral and constitutive part of life, observed in several animals. In humans, the quantity of sleep needed varies from person to person, but it is estimated that, on average, 7 to 8 hours of sleep are required per night for not having impaired body functions [1, 2]. Although sleep mechanisms and functions are still debated, it is an important biological need with implications in the learning process, memory consolidation, emotional stability, and maintenance of cerebral homeostasis [3-6]. The brain displays two types of electrical activity during sleep: 1) slow-wave activity, characterized by Non-Rapid Eye Movement (NREM sleep); and 2) desynchronized brain wave activity, characterized by rapid eye movement and represented by muscle atony and wakeful brain activity (REM sleep) [7].

During a normal night sleep, there are about five complete cycles characterized by electrical activities. Each of these cycles is composed of three phases of NREM sleep (N1, N2, and N3) followed by the REM sleep stage [8].

Stage N1 is the transition from waking to sleep, characterized by slow eye movement and is considered the lightest stage of sleep. Stage N2 comprises about 50% of an individual total sleep time, characterized by a constant decrease in the frequency of the electroencephalogram (EEG). Stage N3 is responsible for about 10 to 20% of an individual sleep time and is considered the deepest sleep stage, being very difficult for the individual to wake up during this phase. REM sleep is responsible for about 20% of the total sleep time. At this stage, due to the resemblance to wakefulness, the EEG is similar to an active and awake person. REM sleep is also called paradoxical sleep, and it is during this stage that vivid dreams occur [8].

Synaptic homeostasis restoration is one of the main theories behind the need for a few hours of sleep. The learning process and the new memories formation during wakefulness, as well as synaptogenesis during development, trigger a synaptic strengthening that causes the destabilization of synaptic homeostasis [9]. This increase in the levels of synaptic strength can lead to cellular stress, due to higher energy consumption, as well as a greater demand for cellular supply; also, there is a reduction in the selectivity of neuronal responses and difficulty in the ability to learn. Sleep leads to a reduction in plasticity in neurons and other cells, restoring the ability to learn and neuronal selectivity, normalizing syn-

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aptic strength and leading to the consolidation and integration of memories [9].

Understanding sleep mechanisms, how it is modulated by internal and external conditions and its impact on synaptic plasticity and cognition, are crucial questions in Neuroscience. Therefore, sleep research in different species may prove to be useful to know evolutionary aspects and it may provide critical insights into fundamental functions and conserved genetic mechanisms underlying sleep regulation. The appearance of sleep and wakefulness in various animal species probably depends on their living environments [7]. The neuronal mechanisms and functions of these processes probably evolve to adapt brain functions to each environment, supporting their behavior, maintaining their nervous system and increasing their performances. In this context, wakefulness is responsible for behaviors that are directly related to motivation and aptitude, such as reproduction, the search for food, and parental care [10]. Likewise, sleep is a quiescent state, which is believed to be necessary for the maintenance of the nervous system and the body, including the system that governs consciousness, development, immunity, learning, and memory [5]. Sleep architecture varies between species since sleep and wake behavior is related to specific environments [10-12]. Some marine mammals and birds have sleep behavior known as one hemispheric, in which a cerebral hemisphere generates activity similar to NREM sleep, while the other side maintains wakefulness, allowing these animals to swim or fly while they are sleeping [13, 14].

Over the last 20 years, zebrafish (*Danio rerio*) has gained attention as a robust model for biomedical research, especially for Neuroscience [15, 16]. This species has genetic and physiological similarities to other vertebrates since zebrafish genes show about 70 % homology with human genes [17]. This animal has an integrated central nervous system, with homologous brain structures, showing a high degree of similarity in neuroanatomical and neurochemical pathways, presenting organizational conservation between zebrafish and human brains. The zebrafish brain is composed of four anatomical structures: telencephalon, diencephalon, midbrain, and hindbrain [18]. Vertebrate brain structures, such as the amygdala, isocortex, and hippocampus show, respectively, similarities with the medial, dorsal, and lateral pallium of zebrafish [18, 19]. However, some functional differences are found, for example, the lateral line is responsible for the sensory system in zebrafish; therefore, this species does not have a sophisticated six-layer isocortex, which in mammals provides the main sensory processes [20]. The thalamus is less prominent in zebrafish than in mammals since this species has a preglomerular complex with specific dopaminergic cells [19, 21]. Studies show that zebrafish have neurotransmitter networks identical to those of the human brain: noradrenergic, serotonergic, dopaminergic, histaminergic, aminergic systems, among others [22, 23]. Furthermore, the similarity of the zebrafish blood-brain barrier to the human brain has already been described, including anatomical compositions, cell junctions, expression of enzymes and ion transporters [24]. At the cellular level, astrocytes, microglia, oligodendrocytes, Purkinje cells, myelin, and motor neurons resemble human cells [25]. Studies on adult zebrafish spinal cord neuronal patterns, neural differentiation, and spinal network development showed similarities to higher-order vertebrates [26]. Therefore, in this review, we describe the main sleep regulators, as well as the impact of sleep deprivation on quality of life. In addition, we discuss the use of zebrafish as a model to investigate sleep mechanisms and their regulation.

2. SLEEP MODULATORS

Sleep control mechanisms are regulated through different brain areas, such as the basal forebrain, thalamus, and hypothalamus. The signals between the different cortical regions and to the periphery are carried out by several neuromodulators, which are known to promote wakefulness or sleep, such as acetylcholine, norepinephrine, dopamine, glutamate, adenosine, melatonin, hypocretin (orexin), gamma-aminobutyric acid (GABA), among others [27]. Different molecules are responsible for promoting distinct aspects of wakefulness. Acetylcholine and norepinephrine are involved in cognitive functions, and novelty and stress experiences [28, 29]. Dopamine, a neurotransmitter involved in many motivated behaviors, is found in an increased concentration in the striatum during the waking and active phase compared to its levels during slow-wave sleep and the resting phase [27]. Hypocretins are hypothalamic neuropeptides, regulated by the hypocretin gene, which have important physiological roles in food intake and energy consumption. However, they are also involved in narcolepsy pathophysiology, increasing the amount of NREM sleep [30].

Glutamatergic and GABAergic pathways have been identified as the wake/sleep-promoting systems in recent studies [31, 32]. Glutamate mediates approximately 75% of the excitatory transmission on the central nervous system, being at higher concentrations during excitation in the waking and REM sleep states [33]. GABA has a dual function in sleep processes, being responsible for promoting both sleep and wakefulness depending on its location and considering the complex interaction between other neurotransmitters [27, 34]. Studies demonstrate that, within the basal forebrain, cholinergic neurons are not responsible for wakefulness independently since they inhibit the cortical synchronization, while GABAergic neurons are directly responsible for cortical desynchronization, which results in wakefulness [31, 32, 35]. On the other hand, in the parafacial zone, GABAergic neurons are responsible to induce deep NREM sleep through cortical synchronization [36, 37].

Melatonin and adenosine are mediators known as sleep inducers [38]. Melatonin is widely used clinically to treat insomnia and normalize circadian rhythms [39-42]. In addition, it also has other physiological effects, such as endogenous, anti-inflammatory [43, 44], antioxidant [45], and immunomodulatory hormone [46, 47]. Furthermore, melatonin is involved in the modulation of affective behaviors and improves memory and cognition [48, 49]. Adenosine is one of the most studied sleep-promoting molecules, and it is known that it is an NREM sleep-promoting factor via inhibition of active wakeful neurons and activation of a subpopulation of sleep-promoting neurons [50]. It has been proposed that its increase would be a signal for the need for sleep, aiming at replenishing the cerebral energy reserves [51, 52]. In 1954, Feldberg and Sherwood [53] showed that intraventricular injection in cats of small amounts of adenosine caused a nat-

ural sleep-like state within a duration of around 30 minutes. In addition, an adenosinergic neuronal population expressing adenosine A_{2A} receptors, necessary to promote NREM sleep, has recently been identified [54]. Selective agonists of adenosine A_{2A} receptors, such as CGS21680, administered in the rat brain, induce NREM sleep [55]. Acting oppositely, caffeine, a non-selective antagonist of adenosine A_1 and A_{2A} receptors, promotes wakefulness [56], showing that adenosinergic modulation is related *per se* to sleep processes.

Several drugs modify the effects of sleep regulators and can induce changes in sleep processes, which could be important to investigate the clinical importance of such compounds. Dopamine agonists, used to treat parkinsonian symptoms, impair wakefulness due to the inhibitory signaling of the dopamine D_2 receptor, while levodopa and amantadine impair sleep by increasing dopaminergic activity [57]. In addition, the β-amyloid and tau proteins, which are involved in neurodegenerative processes of Alzheimer's disease, modulate the expression of hypocretin-1 (orexin-A) and adenosine A_1 receptor, explaining the pathogenesis of certain sleep disorders reported in the disease [58]. Caffeine, a non-selective adenosine receptor antagonist present in energy drinks, can inhibit NREM and REM sleep [51, 52]. Antidepressants that act as selective serotonin 5-HT_{1A} receptor agonists significantly suppress REM sleep [59], while monoamine oxidase inhibitors, serotonin and norepinephrine reuptake, and tricyclic antidepressants, increase the noradrenergic and dopaminergic neurotransmission and activate serotonin 5-HT_2 receptor, causing a decline in the quality of sleep [60]. On the other hand, trazodone and nefazodone, which are antagonists of 5-HT_2 receptors with antidepressant properties, tend to promote sleep and improve its continuity [61]. Abuse drugs are also known to influence sleep patterns. Marijuana use can increase slow-wave sleep time, decreasing REM sleep [62]. Other addictive drugs, such as cocaine, nicotine, opioids, and alcohol, can cause a significant reduction in sleep efficiency and quality [62-66]. In addition, the use of nicotine and opioids increases the latency of sleep onset, unlike alcohol, which causes a reduction [66-68].

3. SLEEP DEPRIVATION

Sleep deprivation occurs when the act of sleeping is inadequate and can still occur if the quality of that sleep is poor, even if a person sleeps more than 8 hours a night. Sleep is determined by the number of excitations or waking up during the night, and its deregulation leads to low alertness, reduced performance, and consequent deterioration of health. Sleep deprivation is extremely common, negatively affecting the individual's quality of life and normal physiological functions, with 20% of the adult population reporting not sleeping well [4]. Among the main reasons for sleep deprivation are a) voluntary behavior, people who stay up late, watching television or on the internet; b) personal obligations, such as work, parents of a newborn, or the care of a sick relative; and c) medical problems, such as sleep apnea [8].

Several sleep disorders are caused by psychoactive drug addiction. Furthermore, some medications can aggravate primary sleep disorders, indirectly affecting sleep. Studies show that sleep deprivation negatively affects general physiological well-being and daily behavior, generating negative impacts on metabolic, immunological, and cognitive health, leading to reduced attention and health-related problems [69-71]. Sleep has a restorative function since it works by facilitating the elimination of metabolic waste from the brain that accumulates during wakefulness. An important study conducted in humans showed that sleep deprivation results in impaired molecular clearance of the human brain; and this one-night clearance failure may not be compensated by another night's sleep [72, 73]. Furthermore, sleep deprivation significantly affects memory consolidation [5, 6, 69, 74] since hippocampal-dependent memories, such as spatial and declarative memory, require slow-wave sleep and are most severely affected by sleep deprivation [3, 75].

4. ZEBRAFISH AS SLEEP MODEL

4.1. Sleep in Zebrafish

Behavioral assessment and EEG data are essential for defining the stages of NREM and REM sleep. However, in some animal species, such as zebrafish, the behavioral criteria are the only definers of sleep, including stereotypical posture, consolidated quiescence at a certain time of the day, and an increase in the excitation threshold after deprivation [10]. The sleep of the zebrafish has not been subdivided into the REM and NREM states, as seen in birds, mammals, and reptiles [76], or depth stages of the sleep, as suggested in Drosophila [77]. However, it is known that this animal has a regulated daytime circadian rhythm, and its sleep state is characterized by periods of inactivity accompanied by an increase in the excitation threshold, preference for resting place, and by the rebound effect of sleep, which causes an increase in slow-wave activity after a forced period of wakefulness [78-80]. In addition, the ontogeny of sleep cycles in zebrafish and humans is remarkably similar due to analogies in genetics, pharmacology, and neuroanatomy [81]. Sleep levels are higher at the beginning of development, and sleep and wake periods gradually consolidate to form the adult sleep pattern [82].

A recent study suggested that there are at least two sleep states in zebrafish, analyzing eye movement, cardiac and muscle activity, along with images of the whole brain activity [83]. The study performed images of fluorescent calcium in larval zebrafish, revealing changes in the pattern of dynamic activity during sleep and wakefulness. In awake fish, highly spontaneous and unsynchronized activity was observed, while highly synchronized outbreaks of activity were observed in the same region during sleep. Synchronous oscillatory neuronal states during sleep resembled cortical activity during NREM sleep in mammals [83]. Sleep test has already been standardized in zebrafish. In a study, larvae were subjected to a light (L) and dark (D) cycle of 14 L:10 D. In this test, the acclimatization period of light for 14 h started at 8 am and the larvae were transferred to the Zebrabox at 4 pm, followed by evaluation for 6 h in the dark, started at 10 pm. The distance traveled and high activity were analyzed as well as the average inactivity to determine the period of sleep at night [84]. In adult animals, cognitive tasks have already been performed to assess the impacts of different sleep deprivation protocols in zebrafish. Analyses of aversive memory through electric shock, object discrimination, and affective

spatial memory related to school have been described as altered in animals submitted to sleep deprivation protocols [85-87]. These studies show the importance of using zebrafish, both in the larval and adult stages, as a model in the analysis of sleep disorders through different behavioral tasks.

4.1.1. Sleep Modulators in Zebrafish

The CNS structure of zebrafish has the main domains found in the mammalian brain, as well as the presence of the same neurotransmitters, such as dopamine, serotonin, norepinephrine, glutamate, GABA, histamine, and acetylcholine has already been described [22, 88-95]. These neuroanatomical and neurochemical findings make the zebrafish an ideal model to study possible changes related to the area of neuroscience, including studies related to sleep disorders that modulate these signal transmission pathways.

Studies have shown that hypocretin, a well-known peptide promoting wakefulness, is conserved and has the same functions in zebrafish, being found in approximately 10 bilateral pairs of glutamatergic neurons in the anterior hypothalamus of larvae up to 5 days post-fertilization (dpf) [79, 96-98]. The zebrafish has a single hypocretin receptor (HcrtR), being expressed in projections of dopaminergic and norepinephrine neurons in the larvae brain. In adults, HcrtR can also be found in serotonergic and histaminergic neurons [96, 97]. Zebrafish studies have shown that hypocretin overexpression causes decreased sleep, and HcrtR mutations lead to sleep fragmentation at night [79, 98]. In addition, the evaluation of resting modulating molecules in mammals, such as barbiturates and benzodiazepines, shows sedative effects in zebrafish larvae [99]. Noradrenergic neurons have also shown importance in the regulation of wakefulness, as well as the neuropeptide neuromedin U (Nmu), the latter being an important promoter of awakening [100-102].

Based on studies that report the functional similarity of neurotransmission systems between mammals and zebrafish, Rihel *et al.* [103] conducted a pharmacological screening of small molecules through rest/wake behavioral analysis. Some behavioral parameters analyzed included the number and duration of rest sessions, rest latency, and wakefulness activity. Among the main findings, the study demonstrated that selective serotonin reuptake inhibitors, such as fluoxetine, fluvoxamine, and paroxetine, reduced arousal in zebrafish. Regarding the adrenergic system, the trials showed that α2- adrenergic agonists, such as clonidine and tizanidine, decreased wakefulness with little effect on rest. On the other hand, activation of β-adrenergic receptors, through exposure to clenbuterol and fenoterol, reduced the total rest at night. β-adrenergic receptor antagonists, such as bopindolol and carvedilol, have increased total rest. Modulation of the dopaminergic system has shown that D2 receptor agonists, such as apomorphine and bromocriptine, reduce wakefulness and increase rest; and D2 receptor antagonists, such as benperidol and droperidol, increase wakefulness as well as rest. Tracazolate, an anxiolytic that acts as an allosteric modulator of the GABAA receptors, and diphenylpyraline, a histamine H1 receptor antagonist, were able to increase the wakefulness activity in zebrafish. Likewise, all NMDA receptor antagonists evaluated, including DCQX and MK-801, dramatically increased wakefulness activity during both day and night [103].

Melatonin plays a role in coordinating circadian rhythm and onset of sleep in zebrafish [104, 105]. In addition to melatonin, QRFP, a neuropeptide from the RFamide family, is also a sleep-promoting agent, being expressed adjacent to HcrtR located in zebrafish glutamatergic neurons [32, 106]. Recent evidence shows that in zebrafish, pharmacological inhibition of 5-HT synthesis and the mutation of tryptophan hydroxylase 2 (tph2), which is necessary for the synthesis of serotonin (5-HT), results in reduced sleep, depth of sleep, and homeostatic response to sleep deprivation [107]. On the other hand, chemogenetic stimulation of 5-HT neurons [108] induces sleep. Sleep test has already been standardized in zebrafish using ethanol as a sleep state modulator. Embryonic exposure to ethanol increased periods of arousal and inactivity [84].

4.1.2. Sleep Deprivation and Disorders in Zebrafish

Sleep deprivation is commonly associated with decreased attention, reduced response to stimuli, and impaired performance in cognitive tasks. Since zebrafish have a behavioral repertoire capable of demonstrating changes that can be caused by sleep deprivation, its use in this model has been relevant. Pinheiro-da-Silva *et al.* [85-87] evaluated the effects of partial (18 L: 06 D) and total (24 L: 00 D) sleep deprivation on the learning performance and memory of the adult zebrafish through an inhibitory avoidance task, using shock as a stimulus aversive, and object discrimination paradigm. The results showed that the total, but not the partial, sleep deprivation significantly impaired the behavioral responses of memory and learning through the two tests performed in comparison to the control group, that remained in the cycle of light established by the laboratory (12 L: 12 D) [85, 87].

Melatonin has also been used in studies to modulate sleep in zebrafish after establishing sleep deprivation in adult animals. Giacomini *et al.* [109] evaluated the effectiveness of melatonin in a memory test, through the inhibitory avoidance task, using shock as an aversive stimulus, in adult animals subjected to sleep deprivation. The authors observed that the control and the melatonin-treated group increased the latency to enter the dark compartment under the normal cycle of 14 L: 10 D, showing a higher cognition retention index in fish treated with melatonin. In contrast, exposure to 24-h light decreased this latency in control fish, indicative of evoked cognitive deficits, while the melatonin-treated group showed greater latency as well as a higher cognitive retention index [109].

Studies using zebrafish to assess neurochemical mechanisms of sleep disorders, such as insomnia and narcolepsy, have already been documented [79, 98, 110, 111]. As previously mentioned, zebrafish have a single receptor for hypocretin, a neuropeptide responsible for regulating arousal, wakefulness, and appetite. The modulation of this receptor triggers phenotypic characteristics of insomnia and narcolepsy. Overexpression of the HcrtR gene inhibits rest and consolidates wakefulness. Like humans with insomnia, hypocretin overexpressed larvae are overexcited and have reduced abilities to initiate and maintain rest in the dark [98]. Similarly, it was seen that transgenic animals with inducible ablation of hypocretin neurons demonstrated that the loss of hypocretin neurons increased HcrtR expression. The results

of this study demonstrated that larvae with ablated hypocretin neurons showed normal locomotor activity, but an increase was seen both in sleep time during the day and in the number of sleep/wake transitions [110]. These data reinforce that zebrafish have regulatory mechanisms that can be modulated to better understand sleep control mechanisms.

Sleep disorders are features of several neurodegenerative diseases. Interrupted sleep is an important characteristic of Alzheimer's Disease (AD), often appearing years before the occurrence of symptoms of cognitive decline. The prolonged wakefulness exacerbates the production of beta-amyloid species (Aβ), one of the main drivers of the progression of AD. Özcan *et al*. [112] hypothesized that Aβ could directly modulate sleep regulatory pathways. To demonstrate this, the authors injected Aβ molecules and peptides into the brain of zebrafish larvae and observed that short Aβ oligomers induce acute wakefulness, while longer Aβ forms induce sleep. According to the authors, these data indicate that Aβ can trigger a bidirectional sleep/wake switch and that changes in the Aβ oligomeric environment of the brain, such as during the progression of AD, can therefore interrupt sleep through changes in acute signaling events [112]. However, zebrafish is not always the best animal model for studying sleep disorders characteristic of neurodegenerative diseases through induction by some agents. Using the oxidized product of a classic neurotoxin, MPP+, which selectively damages dopaminergic neurons in the substantia nigra and induces parkinsonian symptoms, Christensen *et al.* [113] observed that larvae exposed to this neurotoxin exhibit a sleep phenotype inconsistent with human Parkinson's disease (PD), with longer sleep periods and less sleep fragmentation, while the main symptom related to sleep in PD is increased sleep fragmentation [113]. This finding does not preclude the use of zebrafish as a model for this type of study; however, it makes it clear that the use of MPP+ as an inducer of sleep disorders characteristic of PD in this species does not trigger the desired symptoms.

5. EVIDENCE SUMMARY

The use of zebrafish as an experimental model for several areas of study is already well documented, including biochemical [114-116], behavioral [117, 118], and toxicological [119-121], being considered an important model animal for drug screening [122, 123]. Findings in this species have contributed to the development of new technologies and sophisticated methodological strategies, such as the generation of CRISPR-Cas 9 mutants, morpholinos, and microarray technology [124-126], since after genome sequencing of this animal, the presence of 82% of genes related to human diseases was revealed [17]. This species has also been widely used for developmental biology studies since it has external fertilization and reproduction, having a rapid biological development cycle throughout the year. The eggs are relatively large and transparent, and cell division and the formation of a new organism can be observed in real-time [117, 127, 128].

Advances in experimental analysis and the formation of new concepts using model organisms, such as zebrafish, provide insights into sleep and wakefulness modulation through neural and molecular mechanisms. As described in this review, several approaches can be performed using this animal to evaluate the different mechanisms related to the modulation of neurotransmission systems in sleep. However, most studies described in the literature focus on the analysis of mechanisms related to hypocretin and melatonin. It has already been seen that zebrafish have a fast metabolism and great sensitivity to drugs from different families [129-131], so the analysis of the cause or influence of medications and addiction drugs in sleep disorders makes this an important research field to be studied. In addition, there are still many gaps in understanding which need to be filled since sleep and wakefulness involve highly complex brain mechanisms.

Different drugs have significant affinity for various protein targets, which have anatomical sites of action and unique pharmacological properties, resulting in distinct functional modulations related to sleep and wakefulness. Among the classes of drugs that have been little evaluated for their influence on sleep and wakefulness, there are the nootropics. These drugs are known as memory enhancers, being used to restore memory and improve brain performance in patients with encephalopathies [132]. A study using modafinil showed that this nootropic modulates sleep-wake activity in zebrafish larva; however, it is not known through which mechanism this medication exerts its action [133]. Regarding the action of this class in the zebrafish memory, it was demonstrated that the administration of piracetam improved learning in zebrafish without any changes in the behavioral parameters [134]. These findings are important since it is already known that impaired memory and learning are consequences of sleep deprivation.

Addiction drugs also influence sleep, both in induction and increasing wakefulness [62, 65, 66]. However, there are no studies so far that have used different drugs of abuse, such as cocaine, opioids, marijuana, and nicotine, and studied their relationship to sleep disorders in zebrafish. Adult zebrafish have altered locomotor activity when exposed to different concentrations of nicotine and cocaine and have also shown behavioral changes related to abstinence from these drugs [135]. A study carried out using opioids observed that larvae exposed to codeine or morphine presented hypoactive behavior compared to control larvae [136]. Further studies on the influence of these drugs on sleep disorders in zebrafish are a relevant field to be investigated.

CONCLUSION

In conclusion, a better understanding of the molecular and neuronal mechanisms of the main drugs used for sleep modulation and wakefulness will increase our knowledge regarding sleep regulation. In addition, the development of selective therapies related to sleep disorders may contribute to the improvement in the quality of life. The use of animal models, such as zebrafish, will facilitate targeted approaches pointing to critical characteristics that can be shared by sleep circuits in all species.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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