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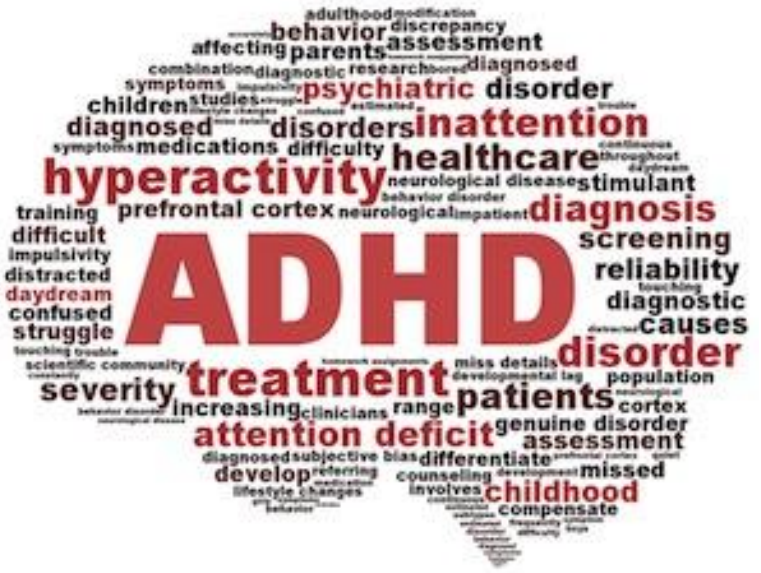
ADHD and the circadian rhythm



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Thesis
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Title page

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Does ADHD medication disturb the circadian rhythm?

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Abstract

Individuals with ADHD always experience difficulty concentrating on a specific task, which interferes with the ability to learn, work and engage in social activities. This is thought to be caused by hypofunction of the dopaminergic system. However, the exact mechanisms is still unknown and a lot of theories exist about the underlying cause. Individuals with ADHD often suffer from sleep problems, which could be caused by their hyperactivity. Some studies however, suggest that it is caused by the stimulant medication. Individuals with ADHD medication had an increase in sleep problems compared to individuals without medication. The exact cause of this is unknown, however some studies suggest that the medication disturbs the circadian rhythm. Multiple studies found that MPH and ATO influenced the expression of certain clock genes, like Per1, Per2 and CLOCK. Further, they found a shift in the SCN rhythm. A different studies suggest however, that ADHD is caused by a mutation in circadian clock genes, instead that the dysregulation is a consequence of the medication. More research is necessary to investigate the underlying mechanism of the development of ADHD and to determine the effects of the medication on the circadian rhythm.

Contents

1. Introduction

From time to time, everyone experiences difficulty to concentrate on their current task or what their teacher is explaining in class. However, some individuals have difficulties with this every day and it can seriously interfere with their ability to learn, work and engage in social activities. This syndrome has become known as attention-deficit hyperactivity disorder or ADHD. Inattention, hyperactivity and impulsiveness are the most common traits associated with ADHD[2].

ADHD is one of the most frequently diagnosed disorders in children, but a lot of controversy exists regarding correct diagnosis. There is no physiological marker for ADHD, so the diagnosis is based on the information provided by the parents and teachers concerning the child's symptoms. This allows for subjectivity in the diagnosis, which might also explain the differences in reported prevalence of ADHD[3]. An objective diagnosis with low false positive and false negative results, is necessary for correct treatment of individuals with ADHD and to prevent overdiagnosis. This way, the individuals that actually need the medication will be treated, so they have better educational and social outcomes. Furthermore, the individuals that do not need to be treated, will not unnecessarily be exposed to the negative side effects of the medication.

Co-morbidity with other developmental disorders, anxiety or depression and learning disabilities is common[2]. Furthermore, 25-50% of the children and more than 50% of adults with ADHD suffer from sleep problems. The simplest explanation for this could be that their hyperactivity prevents them from falling asleep and since sleep is necessary for cognitive function and learning, sleep deprivation could result in exacerbation of the ADHD symptoms. Multiple studies of individuals with ADHD observed an increase in sleep onset latency[4–6], daytime sleepiness[6–8] and REM sleep latency[6,7,9–12] compared to healthy controls.

In this research, the cause for the high co-morbidity of sleep problems in individuals with ADHD is investigated. First, I tried to get more insight into the underlying mechanisms of the hyperactivity symptoms of ADHD, to determine whether it could be responsible for the sleep problems. Furthermore, a different aspect is investigated regarding the circadian rhythm, since this rhythm is very important for a healthy sleep-wake cycle.

2. Attention-deficit hyperactivity disorder (ADHD)

Attention-deficit hyperactivity disorder is a neurodevelopmental disease that usually reveals itself during childhood. Boys are more commonly affected than girls[2] and the worldwide prevalence of ADHD is 5,29%[13]. However, the prevalence rates between multiple different studies varies a lot, ranging from 1-20%[2,3,14]. The wide range can most likely be explained by the use of different methods or the difference in cultural norms and subjectivity of the diagnosis procedure[13]. The diagnosis is based on the information received from parents and teachers concerning the child's symptoms, since no biological marker has yet been found. ADHD is part of a diagnostic category of the Diagnostic and Statistical Manual of mental disorders (DSM-IV), which divides the ADHD in a hyperactive/impulsive or an inattention group. The international classification of diseases (ICD-10) uses hyperkinetic disorder as the diagnostic term and includes features as onset before age 7, hyperactivity, impulsiveness and inattention. Furthermore, it is important for diagnosis that the symptoms must be present in at least 2 settings, such as home and school. Finally, the symptoms result in impairment[2], which could include learning difficulties or social problems. 50-60% of children with ADHD experience rejection by their peers[15,16]. This rejection has been linked to specific play behaviors, like being inattentive during organized games and violating the rules. Further traits are being bossy, intrusive, inflexible, controlling, annoying, explosive, argumentative and easily frustrated[16–18]. These social deficits make it hard to make friends, which leads to social isolation. Without social interactions they cannot practice their social skills, which leads to more rejection[16]. Thus, ADHD has a large impact on social functioning and relationships. The remaining chapters of this thesis will focus more on the neurological aspect of ADHD.

As a multifactorial disease, ADHD is caused by both environmental and genetic factors. Examples of environmental factors that are associated with ADHD are maternal smoking, exposure to cocaine or alcohol during pregnancy, maternal anaemia, low birth weight, prematurity and small head circumference. Furthermore, illnesses during childhood like meningitis, encephalitis, thyroid disease, autoimmunity, metabolic disorders are also associated with ADHD[19]. These environmental influences together with a genetic predisposition, can lead to the development of ADHD. The mean heritability of ADHD is 60-77%, according to multiple twin studies[19,20]. Linkage and association studies determined a number of genes, which seem to be important in the development of ADHD. The most important genes are those for the dopamine D4 and D5 receptor, dopamine transporter 1 (DAT1), dopamine β-hydroxylase, synaptosomal-associated protein 25 (SNAP-25), serotonin 1B receptor and the serotonin transporter[19–21]. The involvement of multiple genes of the dopaminergic system, suggest a strong influence of the dopaminergic neurotransmission in the development of ADHD.

3. Dopaminergic system

Dopamine is a neurotransmitter and belongs to the category amines[22]. It is synthesized from tyrosine together with noradrenaline and adrenaline, which are collectively called catecholamines[23]. Dopaminergic neurons originate from the substantia nigra and ventral tegmental area (VTA) in the midbrain and terminate in the prefrontal cortex and parts of the limbic system, such as the basal nuclei (basal ganglia) which contains the nucleus accumbens and the striatum. Dopaminergic neurons are involved in motor control and the "reward" system[23]. When these neurons are not able to produce enough dopamine, dysfunctions in motor control occur. An example of this is Parkinson's disease, in which cell death of the neurons of the substantia nigra is observed. This results in a decrease in dopamine producion, which leads to symptoms as slowness of movements and difficulty with walking[24]. Furthermore, a model suggesting a direct and indirect pathway is currently used to explain the inhibition and stimulation of movement. The direct pathway is suggested to inhibit GABAergic neurons in the basal ganglia, such as the substantia nigra reticulata (SNr), which leads to disinhibition of the thalamocortical and brainstem circuitry and promotes movement. In contrast, the indirect pathway inhibits movement by increasing SNr activity via the subthalamic nucleus (STN), which inhibits downstream circuitry and movement[25]. Thus, it seems that a balance between both pathways is necessary for motor control.

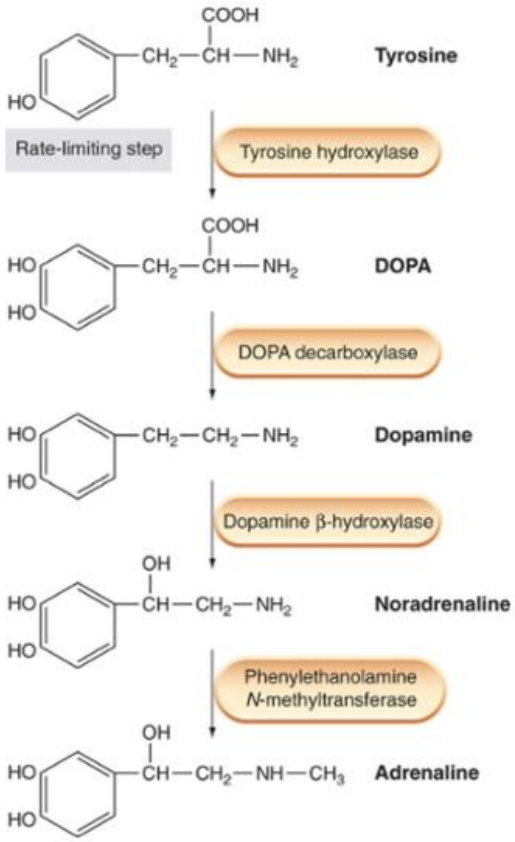

Figure 1: Biosynthesis of catecholamines. *Dopamine, noradrenaline and adrenaline are all synthesized from tyrosine. First tyrosine is converted to DOPA through tyrosine hydroxylase, which is the rate limiting step. Then DOPA is converted to dopamine by DOPA decarboxylase. Further, noradrenergic neurons contain the enzyme dopamine ß-hydroxylase, which converts dopamine to noradrenaline. And adrenergic neurons contain another enzyme called phenylethanolamine N-Methyltransferase, which converts noradrenaline to adrenaline*[26]*.*

During dopamine synthesis, tyrosine is first converted to DOPA by tyrosine hydroxylase and then DOPA decarboxylase converts DOPA further into dopamine[23] (see figure 1). Dopaminergic neurons do not contain β-hydroxylase, so dopamine is not converted to noradrenaline. After synthesis, dopamine is stored in vesicles by the vesicular monoamine transporter (VMAT). Membrane depolarization leads to

calcium influx, which stimulates exocytosis of the dopamine vesicles. After release, dopamine is transported back into the pre-synaptic cell by dopamine transporters (DAT). There it is repackaged in vesicles or metabolized by monoamine oxidase (MAO) to DOPAC, which is excreted via the urinary tract[27]. Dopamine can bind to receptors on the post-synaptic cell and induce a response (see figure 2). Dopamine receptors are G-protein coupled receptors and are found in the central nervous system[23].

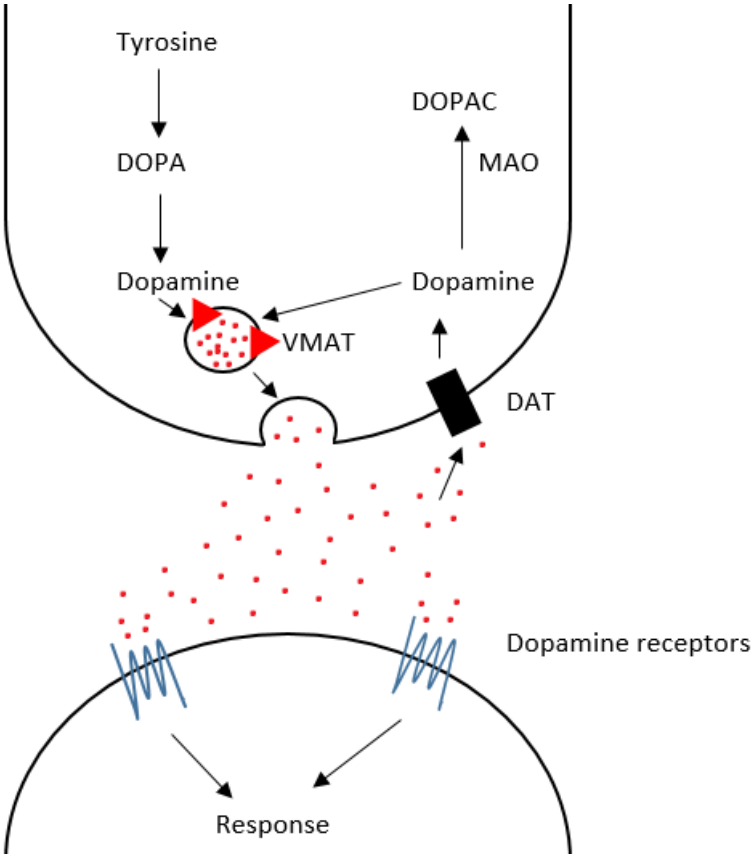

***Figure 2: Dopamine life cycle**. Dopamine is synthesized from tyrosine and transported into vesicles by VMAT. After stimulation, the vesicle fused with the cell membrane and dopamine is released into the synaptic cleft. Dopamine can then bind to receptors on the post-synaptic cell and induce a response. Dopamine is transported back into the pre-synaptic cell by the dopamine transporter (DAT) where it can be recycled, by transporting it back into vesicles, or dopamine is metabolized by MAO to DOPAC and excreted via the urinary tract.*

Another neurotransmitter is noradrenaline, which is synthesized from dopamine through β-hydroxylase in noradrenergic neurons. Noradrenergic neurons are found in the pons and influence other parts of the central nervous system via axons. The locus coerulus (LC) is a cluster of noradrenergic neurons in the pons, which influence the cortex, hippocampus, thalamus, hypothalamus and cerebellum. Furthermore, the amygdala is influenced by neurons close to the LC. During sleep, the LC neurons are silent and firing increases with behavioral arousal.

4. Dopaminergic dysfunction in ADHD

Dysfunction of dopamine neurotransmission is thought to be the underlying cause of the symptoms of ADHD. The exact mechanism is still unknown and a lot of different theories exist. Most researchers agree that the symptoms of ADHD are caused by hypofunction of the dopamine system[28]. This theory is consistent with the positive effects on ADHD symptoms of dopamine increasing medication, like methylphenidate (Ritalin™). Hypofunction could result from decreased dopamine synthesis, overexpression of DAT or overactive DAT, which would result in a decreased amount of dopamine in the synaptic cleft. Furthermore, over activity of MAO could lead to increased dopamine degradation and mutations in the dopamine receptors itself could influence the post-synaptic signaling. Studies have tried to get more insight into the mechanisms behind the disturbed dopamine signaling and Forssberg et al. found a decrease of dopamine synthesis in ADHD patients compared to healthy controls. The values were particularly low in subcortical regions and the low synthesis correlated with the severity of the symptoms. Furthermore, they found a reduced DAT density in the midbrain and speculated that it is a compensational result of the low dopamine synthesis[29]. Other studies, found an increase in DAT density[30,31], which could cause the hypofunction of dopamine by transporting it back into the pre-synaptic cell before dopamine can bind to the receptors and induce a response. However, an increase in DAT expression could also be a response to an increased dopamine concentration in the synaptic cleft. Furthermore, it was unclear whether the individuals that were used for this study, had received any stimulant drugs in the past. The use of stimulant drugs could alter the DAT expression for the long term[30]. Finally, other studies found an increase in striatal DAT activity[32–34], which has been associated with decreased dopaminergic function, hyperactivity and deficits in inhibitory behavior[34–36]. Thus, there are a lot of different theories about the underlying mechanism of the dopaminergic dysfunction and further research is necessary. The male spontaneously hypertensive rat (SHR) model is found to be well suited for the three core symptoms of ADHD. The dopaminergic neurotransmitter system is hypofunctional in these rats, which is consistent with the theory that ADHD is caused by decreased dopaminergic function[37]. However, this dopamine dysfunction seems to be caused by an impairment in the second messenger systems, not in the dopamine life cycle itself. A better model has yet to be found.

Robert D. Oades[38] proposed a more complex mechanism, in which the balance between the monoaminergic neurotransmitters dopamine, noradrenaline and serotonin is disturbed. He states that dopamine may be hyperfunctional compared to noradrenaline and hypofunctional in respect to serotonin. The activity of noradrenaline is found to be decreased in individuals with ADHD compared to healthy controls[39], which disturbs the balance with dopamine. In contrast, serotonin seems to be increased in ADHD patients[40].

ADHD seems to be caused by a lot of different factors, which disturb the balance between neurotransmitters in the brain. It is a very complex disorder and most likely very heterogeneous, since a lot of different factors are involved. For example, a certain dysregulation in one patient could lead to the symptoms of ADHD and a slightly different regulation in a different patient could results in the same symptoms. If this is the case, medicating ADHD patients would be very difficult and requires personalized medicine. Current medication influences the dopaminergic and noradrenergic systems. Methylphenidate is most often used and is a DAT inhibitor. Furthermore, atomoxetine is sometimes given when MPH has no effect, which inhibits the reuptake of noradrenaline. This thesis focusses mostly on the dopaminergic system and the mechanism of methylphenidate (MPH).

5. ADHD medication

Methylphenidate hydrochloride (Ritalin) reduces symptoms in up to 70% of the children and is one of the most effective treatments for ADHD[41,42]. MPH is a psychostimulant drug, which significantly reduces the motor activity level in ADHD patients[43]. Furthermore, it shows behavioral and cognitive function improvement. The effects on motor activity last for approximately 7-8 hours and the effects on attention for 2-3 hours[30]. MPH binds to and blocks the dopamine and noradrenaline reuptake transporters, which suggests that there may also be a role for noradrenaline in the alleviation of the symptoms[30]. Finally, a study suggests that MPH not only inhibits the DAT, but also functions as a reverse agonist which leads to an even stronger effect on the extracellular dopamine concentration[44]. A reverse agonist has the opposite effect of an agonist, so the normal function of the DAT is to transport dopamine from the synaptic cleft back into the pre-synaptic cell. A reverse agonist would reverse this transport, so dopamine gets transported from the pre-synaptic cell into the synaptic cleft.

It seems counter-intuitive to treat ADHD with a psychostimulant drug. The exact mechanism of ADHD pathology is still unclear and the hypofunctional dopamine transmission hypothesis is mostly based on the observation of positive effects of stimulant drugs. Dopamine has been implicated to facilitate movement. Individuals that suffer from Parkinson's disease are known to have a decreased dopamine transmission. How does a decreased dopamine transmission in ADHD result in increased motor activity? And through what mechanism does the increase in dopamine by stimulant drugs result in reduced motor activity? The exact answers to these questions are still unknown, however hypothesized is that the increase of dopamine by stimulant drugs mostly influences the indirect pathway in the basal ganglia[45]. The basal ganglia receive input from the striatum and subthalmic nucleus (STN). The basal ganglia then processes and adjusts the input, before sending a signal to the cerebral cortex. These information pathways are distributed in the direct and the indirect pathway. The direct pathway stimulates movement via direct innervation of the striatum to the basal ganglia. In contrast, the indirect pathway inhibits (unwanted) movement by sending a signal via the globus pallidus and STN to the basal ganglia. Hypothesized is that in ADHD the striatopallidal indirect pathway is affected, which leads to an impaired inhibition in movement and motor hyperactivity. By stimulating this pathway with dopamine releasing medication, it decreases the hyperactivity[45].

As mentioned earlier, individuals with ADHD often suffer from sleep problems, such as increased sleep onset latency and REM sleep latency. Hypothesized was that the hyperactivity caused these sleep problems, so medication with stimulant drugs which significantly reduce the hyperactivity should result in a decrease in sleep problems. However, this does not seem to be true. Some studies compared individuals with medication for ADHD to individuals without medication and they discovered that individuals with ADHD medication had an increased rate of sleep problems compared to the unmedicated group[46,47]. The cause for this is still unknown, however some studies suggest that the ADHD medication affects the circadian rhythm and thereby disturbs the sleep-wake cycle[48,49]. Furthermore, dim light melatonin onset (DLMO) is a reliable marker for circadian function[50] and seems to be delayed in children with ADHD[6].

6. Circadian rhythm

Most animals' behavior is influenced by the circadian rhythm, which literally translated means approximately (circa) a day (dies). The actual behavior varies between species, like whether an animal is active during daylight hours or night. Furthermore, most processes in the body are also influenced by the circadian rhythm, like the fluctuations in certain hormone levels. Without any external stimuli the biological clock maintains an approximately 24 hour rhythm. This is called "free running" and can eventually lead to a shift from daytime activity to nighttime activity. For example, if the biological clock maintains a rhythm of 24,5 hours per day, which is half an hour longer than a "normal" day, the day and night rhythm starts to shift. Therefore, external stimuli like Light and darkness synchronize the biological clock to the day and night cycle[51].

The biological clock is located in a region of the hypothalamus, called the suprachiasmatic nuclei (SCN). Each SCN cell is able to sustain the circadian rhythm when they are removed from innervation of the rest of the brain, however they can no longer be synchronized by the light-dark cycle. Completely removing the SCN, result in abolishment of the biological rhythm. The rhythm is caused by transcription and translation of the circadian locomotor output cycles kaput (CLOCK) gene. During transcription, mRNA is produced and translated into proteins. These proteins cause a negative feedback, resulting in a decrease in gene expression and protein concentration. Through the decrease in proteins, the negative feedback is eliminated and gene expression increases. This entire cycle takes about 24 hours and thus establishes a circadian rhythm[51].

The SCN is synchronized with the light-dark cycle via the retinohypothalmic tract. This tract consists of axons from recently discovered photoreceptor ganglion cells in the retina that directly innervate SCN neurons. An animal with a mutation in the rods and cones still demonstrates biological clock synchronization by the light-dark cycle but if the eye is completely removed, free running is observed. Melatonin is an important messenger of the light-dark stimulus. The secretion of melatonin is inhibited by light, so melatonin is always highest during night. This also applies to night active animals, however the influence of melatonin on behavior differs between day and night active animals[51].

This thesis focusses on the dopaminergic dysfunction in ADHD and the result of stimulating medication on sleep. Dopamine seems to have a function on the gene transcript regulation of circadian clock genes. And daily injection with amphetamine, which also increases dopamine function, seems to shift the rhythms of clock genes per1 and per2[52].

7. Circadian rhythm dysfunction, cause or result of ADHD

There are several lines of evidence that there is a connection between the circadian rhythm and ADHD treatment. For example, Baird et al. showed that there was no change in rhythmic PER1 expression in the SCN by daily methylphenidate (MPH) or atomoxetine (ATO) treatment. However, there was a reduction in SCN PER2 expression by both MPH and ATO. PER2 is an important molecular component of the master circadian clock, when its expression is altered it can lead to dysregulation of the circadian rhythm. In the paraventricular nucleus (PVN) of the hypothalamus, a general upregulation of PER1 by MPH and a downregulation by ATO was observed. Furthermore, a significant reduction in PER2 expression by both MPH and ATO was seen. No significant effects on CLOCK, PER1 and PER2 were observed in the hippocampus, amygdala and cortical areas. However, an increase in c-Fos expression in the basolateral amygdala and three cortical regions by MPH was seen. In the caudate putamen MPH and ATO significantly increased PER2 expression and the peak expression of CLOCK was earlier, which suggests a shift in the expression rhythm. The timing of PER2 expression was delayed by MPH treatment[49]. The effects on clock genes by MPH and ATO suggests they can influence the circadian rhythm, however the effect seems to be region and protein specific since in some areas of the brain certain genes are upregulated while they are downregulated in other regions. Furthermore, MPH and ATO can both affect the clock genes, however in some cases with an opposite effect. The mechanism behind this is still unclear and needs further research. The effect observed on PER2 expression in the SCN indicates modulation of the master circadian clock's function, which could be a cause for the dysregulation of the circadian rhythm and in turn the sleep problems found in ADHD patients.

Another study, suggested that MPH can alter sleep and the circadian rhythm by influencing the SCN clock of healthy adult mice. They found increased activity levels, particularly in the late part of the active phase. Furthermore, the animals that were treated with MPH started their activity significantly later than control animals. Sleep onset was also delayed and wake time increased. During dark-dark conditions, the free running period was lengthened in comparison to their baseline. The parameters of the SCN were shifted, which suggests a delay in SCN rhythm[53]. All these results suggest a shift in the circadian rhythm of the MPH treated mice, which could explain the sleep problems of individuals with ADHD that receive MPH. The exact influence of dopamine on the circadian rhythm is unknown. However, it is found that mice which lack the dopamine 1 receptor have a disturbed circadian rhythm and the rhythm of PER2 was suppressed[54]. This is in contrast with the hypothesis that the medication of ADHD caused the circadian dysfunction, since the medication should increase the dopamine signaling and therefore rescue the circadian rhythm. The study of Bussi et al. suggests that it is the lack of rhythmicity of the dopamine release that influences the rhythm of the circadian clock[55]. Furthermore, dopamine is thought to be important to determine day- and night by the retina and seems to have an opposite effect to melatonin. Melatonin is highest during night and is degraded by light and dopamine is high during the day[56]. This agrees with the hypothesis that it might be the dopamine rhythmicity that is important for correct circadian clock function, which could be disturbed by the ADHD medication.

The study of O'Keeffe et al[48] focusses on another medicine for ADHD, the noradrenaline reuptake inhibitor atomoxetine. They found that ATO phase-shifts the circadian clock in mice. First, they investigated the effects of ATO on the free-running rhythms in light-light and dark-dark conditions. Different times of treatment during the circadian cycle were used, indicated by central time (CT). Only a significant effect was found at CT6. A phase delay was observed at CT6 in light-light conditions and a phase advance in dark-dark conditions, which suggests a shift in the circadian rhythm. Furthermore, they examined the effects of ATO on the expression of CLOCK, PER2, c-Fos and BMAL1 in the SCN at CT6 in both light-light and dark-dark conditions. No effect was found on PER2 and BMAL1, but treatment with ATO at CT6 in light-light conditions resulted in a decrease in c-Fos and CLOCK expression in the SCN. Other noradrenaline reuptake inhibitors exerted similar effects as ATO, but when animals were pretreated with α-adrenergic blocker prazosin the phase shifts were attenuated.

Thus, this indicates that the effect on the circadian rhythm is caused by the increased noradrenaline concentration. Furthermore, the timing of the medication seems to be important, agreeing with the study of Bussi et al. that the rhythmicity of the hormones is important for the circadian rhythm.

These studies suggest that the ADHD medication may cause circadian dysregulation, which might result in sleep problems. However, these studies used healthy mice and the results might differ in patients with ADHD, since the neurotransmission in these patients already seems to be dysregulated. In contrast to the previous studies, Huang et al[57] suggest that the underlying cause of ADHD is a dysregulation of the circadian rhythm, instead of a consequence of the medication. This is the exact opposite as our hypothesis. They used zebrafish with a mutation in the per1b (PER1) clock gene and observed that they exhibited similar symptoms as humans with ADHD. They displayed hyperactivity, measured by the amount and velocity of swimming. To make sure it was indeed caused by the per1b mutation, the hyperactivity was rescued by injecting functional per1b mRNAs. To investigate learning and memory deficits, they measured the ability to learn and remember the avoidance of an electrical shock. They concluded that per1b mutant fish had a decreased ability to learn and form long term memories, which indicated a deficit in learning and memory ability. Furthermore, they discovered an impulsivity-like phenotype by performing a two-choice serial reaction-time task. Per1b influences the dopamine metabolism by influencing enzymes and so directly regulates dopamine concentrations, so it is not surprising they found a disruption of the dopamine transmission. They discovered significant lower dopamine levels in the per1b mutant compared to the wild-type. MOA and β-hydroxylase are rhythmically expressed and were upregulated in the per1b mutant compared to the wild-type, which leads to lower dopamine levels. Furthermore, dopaminergic neuron development in areas that have been implicated to influence cognition, motivation, learning and motor activity were found to be significantly decreased in per1b mutants compared to wild-type. The symptoms of the per1b mutants could be rescued by ADHD drugs like MPH. To confirm that these findings also apply to mammals, they used Per1 knock-out mice. These mice also displayed hyperactive and impulsive behavior and during the water maze experiment impaired learning and memory was observed.

A number of studies seem to support the theory that there is a connection between ADHD and the circadian rhythm. However, whether the ADHD medication is the cause of circadian rhythm dysregulation or that mutations in clock genes are responsible for the development of ADHD, is still unclear. Both seem to be true, regarding the articles referred above and because it is such a complex mechanism more research is necessary. Maybe mutation in clock genes are indeed a risk factor for developing ADHD, since they can influence the dopaminergic transmission. Furthermore, ADHD medication given at certain times can further disturb the circadian rhythm. It might help if the natural dopamine rhythm is taken into account in ADHD drug administration, so phase-shifts will not occur.

In contrary to the negative effects of medication on sleep in individuals with ADHD, students seem to use these circadian dysregulations for study purposes. When asked, most students say they use medication as MPH to be able to stay awake longer. Furthermore, the cognitive boost and concentration enhancement makes it easier for them to excel in classes in this competitive and stressful society[58].

8. Use of stimulant drugs by healthy students

Use of “doping” in athletes is commonly known and regulations are already set in place. However, using drugs by students for cognitive enhancement is something that is observed recently and there are no international policies for universities how to handle this. In some universities it is officially recognized as cheating and in others no regulations are in place[59]. The article of the Guardian: “Students used to take drugs to get high. Now they take them to get higher grades” says that students feel that they need some help to deal with the pressure of getting good grades, so they will be able to get a job later. They say it does not make them more intelligent, but just helps them study longer and to not get distracted[60]. Discussions about the acceptability of cognitive enhancement drugs are mainly focused on 4 themes. First, regard for authenticity, which implies that the results of students using drugs do not reflect that individuals true abilities. Second, there are concerns of safety and side-effects. Third is unfairness in relation to the students that work hard without help of drugs. And finally, the proper use of medication. Most people believe that prescription drugs are only for treatment of diseased and are not to be used by healthy people[59].

The literature on the effects of the drugs on students is scarce, since there is not much control in the amount and time the drugs are used. Furthermore, taking stimulant medication while there is no medical reason (misuse) is officially not accepted, so students keep it a secret. The number of misuse is probably also underestimated, since abuse is underreported by physicians. The WHO saw an increase in number of prescriptions per year, which could be explained by the increase in ADHD diagnosis. However, the consumption seems to exceed the prescriptions, which indicates abuse[61]. Students with ADHD are often seduced into giving away, sell or trade their medication. Also, some students admitted stealing someone’s ADHD medication[58].

Regulations about use of cognitive enhancers by healthy individuals should be made, so everyone is treated equally. Only students with a medical reason should be able to take the medication. If it is forbidden to use prescription drugs by healthy individuals and tests before exams are implemented, individuals with ADHD will not be pressured into selling or giving away their medication. Furthermore, students that do not want to use drugs will not be coerced into using them to keep up.

9. Conclusion

Individuals with ADHD often suffer from sleep problems. It seems logical that this is caused by their hyperactivity and should be positively influenced by their medication. However, studies found that individuals with ADHD that were medicated had more sleep problems than the unmedicated group. Some studies suggested that the increase in sleep problems was caused by dysregulation of the circadian rhythm. MPH and ATO were found to influence certain clock genes, like Per1, Per2 and CLOCK in different areas of the brain. Furthermore, the parameters of the SCN were shifted after MPH treatment in mice, which indicates a shift in circadian rhythm and could cause the sleep problems in individuals with ADHD. Finally, ATO also seemed to phase-shift the circadian clock. A contrary investigation, discovered that mutations in the per1b gene in zebrafish lead to an ADHD-like phenotype. This suggests that the underlying cause of ADHD is the dysregulation of the circadian rhythm, instead of a consequence of the medication. More research should be performed to investigate which hypothesis is true. It might improve sleep problems to adjust the medication to the normal circadian rhythm of dopamine and the other neurotransmitters, however this would be very difficult.

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