Chapter

Serotonin, Sleep and Depression: A Hypothesis

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Abstract

For most cases of endogenous depression (major depression), the hypothesis of monoamine deficiency, despite a number of limitations it faces, is still considered the most acceptable explanation. The main difficulty faced by this hypothesis is the *reason* for the decrease in the level of cerebral monoamines (primarily serotonin) during depression. It is assumed either increased activity of the MAO enzyme, which metabolizes serotonin, or a mutation with the loss of function of the gene of the Tph-2 enzyme, which synthesizes serotonin, as possible causes. In this review, a third cause is proposed, which can explain a number of cases of «spontaneous» onset of depressive symptoms in apparently healthy people, as well as links the hypotheses of "monoamine deficiency" and "disturbances in circadian rhythms." It is assumed that the formation of endogenous depression is due to a combination of two factors: a reduced "basal" level of cerebral serotonin and excessively long pre-morning periods of REM sleep, during which the release of cerebral monoamines stops altogether. As a possible way to of non-drug treatment of depression, not deprivation, but fragmentation of this phase of sleep is suggested, that is much easier for patients to tolerate.

Keywords: serotonin, sleep, rem sleep, depression, monoamine hypothesis

1. Introduction

A hypothesis is put forward according to which two factors play an important role in the formation of a number of cases of so-called "endogenous" (major) depression. First, the initially lowered (but within the reaction norm) level of cerebral serotonin, reflecting the gene polymorphisms of the human population. Second, the excessively long pre-morning periods of REM sleep associated with the "pressure of civilization" on the natural structure of the human wakefulness-sleep cycle, during which the release of cerebral monoamines stops altogether. It is a combination of these two factors that can lead to the emotional imbalance seen in depression.

2. Serotonin and sleep

Serotonin (5-HT) is one of the oldest and most important mediators in the central nervous system, participating in a wide range of behavioral, physiological and pathological processes. The history of its study goes back about 70 years, nevertheless, serotonin remains one of the most mysterious neurotransmitters.

As is known, the largest accumulation of serotonergic neurons in the brain is observed in the dorsal raphe nuclei (DRN) and the pons varolii (zones B6 and B7 according to Dahlström & Fuxe [1]). The total number of such cells in human brain is relatively small - about one hundred thousand. The serotonergic system has two characteristics: first, the unusually numerous ramifications of its axons (up to a million bifurcations of a single axon). Secondly, the extraordinary variety of types (at least 7) and subtypes (at least 14; some researchers even count more than 20) of their receptors, among which there are both membrane depolarizing (subtypes 5-HT2A-C, 5-HT3, 5-HT6, 5-HT7) and hyperpolarizing it (5-HT1A,B). Due to the abundant "treelike" branching, several hundred thousands of serotonergic neurons of the brain stem innervate tens of billions of other neurons in the human brain: practically all the nerve cells of the neocortex, hippocampus, striatum, and hypothalamus, other parts of the brain as well as motor neurons of the spinal cord [1, 2]. Only the upper olive complex (part of the auditory system) and the optic chiasm are devoid of serotonin afferents [3]. And due to the receptor diversity, ligands of serotonin receptors can effect both activating and inhibitory processes on the brain and behavior in general.

The role of serotonin transmission in the regulation of wakefulness and sleep was first identified by the work of Michel Jouvet and his laboratory in Lyon, France. In these experiments of the classic of world somnology, performed on cats using primitive technologies of the 60s - early 70s of the last century, the following was shown. Intracerebral administration of serotonin, or electro-stimulation of the DRN or the median raphe nucleus (MnRN), where most 5-HT neurons in the brain are located, induces a short period of paradoxical (REM) sleep, followed by prolonged deep slow-wave sleep (NREM). If, on the contrary, the level of cerebral serotonin is reduced by systemic administration of parachlorophenylalanine (PCPA), which blocks serotonin synthesis, or by destruction of the MnRN, both phases of sleep are sharply reduced. This insomnia lasts at least 10 days. In this case, effect of PCPA is eliminated by the administration of the precursor of serotonin - 5-hydroxytryptophan. These and other early experiments served as the basis for Michel Jouvet's hypothesis about serotonin as "somnotonin" (as it was then called by the Swiss somnologist Werner Koella), the main factor in slow wave sleep [4]. However, further experiments performed in the same laboratory of Jouvet with electrical stimulation and reversible shutdown of DRN neurons caused by local tissue cooling to 10 °C, pointed, on the contrary, to serotonin as a factor of wakefulness. Eventually, it was proved that this hypothesis of Jouvet was wrong - in particular, insomnia caused by suppression of serotonergic neurotransmission was associated with a disorder of thermoregulation, a drop in body temperature, which led to an increase in the motor activity of cats to warm up [5]. And the insomnia that occurs in experimental rats and cats as a result of the administration of PCPA, as it turned out, is the result of a sharp increase in sensitivity to the surrounding animal stimuli, and not a disorder of the regulation of the wakefulness-sleep cycle [6].

Summing up the results of many years of research, a disciple of Michel Jouvet, Raymond Cespuglio, suggested that serotonin may be involved in the regulation of the wakefulness-sleep cycle in two different ways: in wakefulness serotonin is realized on the presynaptic membrane of the 5-HT neurons and promotes the formation and accumulation in target cells hypnogenic neuropeptides: vasointestinal polypeptide (VIP), corticotropin-like intermediate lobe peptide (CLIP), substance P (SP); in the subsequent period of sleep, under the influence of these peptides, dendritic (nonsynaptic) realization of serotonin in the nuclei of the raphe occurs and its binding to the 5-HT1B autoreceptors, as a result of which the synaptic release of serotonin is weakened and stopped [3]. However, this hypothesis also has not received convincing experimental confirmation [6].

Experiments with extracellular registration have shown that most serotonergic neurons are very active in the waking state, and during the transition to sleep and further into deep NREM sleep, they progressively slow down their activity and completely "silence" immediately before the transition to REM sleep. Thorough studies of the activity of not only large and medium-sized, but also small cells of the dorsal raphe of the model mouse brain in the wake–sleep cycle, carried out by Jouvet's disciple Kazuya Sakai, revealed a high anatomical, neurochemical and functional heterogeneity of these neurons. The majority of neurons in this area (52%) are indeed serotonergic (5-HT/DR), and almost all of them (48%) are active only in wakefulness, but a significant part (25% of all cells) are active in sleep, and judging by the spike shape, 19% of them are GABAergic, and only 6% are serotonergic [7]. Apparently, serotonin neurons are mainly responsible for maintaining calm (relaxed) wakefulness; thus, according to some data, they are most active during food consumption and reduce the frequency of impulses with increased behavioral activation [5].

Agonists of all serotonin receptors stimulate wakefulness and suppress NREM and REM sleep when administered systemically or intraventricularly. In this case, the activation of wakefulness occurs by depolarizing the histaminergic tuberomammillary neurons of the posterior hypothalamus, as well as GABA/parvalbumin-containing neurons of the basal forebrain region, which project into the hippocampus and neocortex. Suppression of NREM is carried out mainly by inhibition of neurons in the "sleep center" VLPO, mediated by the 5-HT1A receptor [5]. And the suppression of REM sleep occurs due to inhibition of cholinergic REM-on neurons of the pons [5].

With direct microinjection of inhibitory receptor 5-HT1A agonists into the dorsal raphe nuclei, an increase in REM sleep occurs, whereas similar injections of inhibitory autoreceptor 5-HT1B agonists and activating 5-HT2A/C, 5-HT3 and 5-HT7 receptors suppress REM sleep, which is consistent with the concept of the need for inhibition of 5-HT neurons to trigger REM sleep [8]. Systemic administration of non-selective antagonists of the 5-HT2A/C receptors, selective antagonists or reversible agonists of the 5-HT2A receptor in laboratory rats and mice, healthy subjects and patients with primary or comorbid insomnia causes an increase in NREM sleep, which, again, is consistent with the idea of the participation of 5-HT neurons in maintaining wakefulness [6].

Thus, according to the results of neural and pharmacological studies, serotonin seemed finally established as the status of a wakefulness mediator along with other monoamines (norepinephrine, dopamine, histamine), as well as acetylcholine and glutamate. The main source of serotonin - the DRN – were introduced on diagrams as one of the clusters of the reticular ascending activating system [9, 10]. It has also been shown to play an important role in the negative regulation of REM sleep: without turning off serotonin transmission, neither initiation nor maintenance of REM sleep is possible [6].

In this case, selective shutdown of serotonergic transmission should suppress wakefulness by increasing NREM sleep. Such a methodological opportunity appeared with the introduction of molecular genetic and other newest innovative techniques into neurophysiology. It was found that the brain has its own special isoform of the enzyme tryptophan hydroxylase - Tph2, which converts the amino acid tryptophan, which is supplied to the body with protein food, into 5-hydroxytryptophan, a precursor of serotonin, and encoded by a separate gene. This discovery made it possible to create knockout mice for this gene, in which the content of cerebral serotonin does not exceed 4% of its content in the brain of control mice (that is, practically absent). Figuratively describing the phenotype of such mice, which grew up "without serotonin in their brain", can be named as "evil dwarfs."

They are fertile and females have milk, but they do not care for their offspring, and therefore half of their offspring dies [11, 12]. Disorders of the wakefulness-sleep cycle in these mutants are limited, judging by the results of registration of locomotor activity, to a slight increase in sleep and suppression of wakefulness in daylight (daytime), which seems to correspond with the above hypothesis [13].

At the same time, in another study on genetically modified mice with the homozygous Tph2 mutation (intact neurons, but complete absence of serotonin in the central nervous system) and polysomnographic registration, the following was found. A small (but statistically significant) decrease in the duration of NREM sleep and a corresponding increase in active wakefulness in mutant animals compared with control occurred only when the light was turned on and off. Apparently, the absence of serotonin increases the reactivity of the animal to light stimulation. It was also shown that the sleep of the mutants was less fragmented. No further disturbances in the wake–sleep cycle were identified. In this series of experiments, the absence of serotonin caused only very small changes, not confirming the original hypothesis [14].

However, Tph2 knockout mice cannot serve as an adequate model for studying the role of serotonin in the regulation of the wakefulness-sleep cycle, since it is unclear whether the revealed phenotypic changes are the result of abnormal development, compensation for the lack of serotonin by other transmitters, or, indeed, impaired neurotransmission in adults. To solve this problem, a method was developed to turn off the expression of the Tph2 gene by microinjection of its blocker directly into the tissue of the raphe nuclei of the midbrain and pons in the genetically created mouse strain [15]. By visual analysis of video recordings, it was possible to reveal an increased level of motor activity, especially noticeable in the night (active) phase of the nychthemeron, when in the second half of the night the control individuals experienced a period of decreased activity, called by the authors "siesta". In mice with blocked serotonergic transmission, such periods were absent altogether; they ran almost continuously all night [15]. Thus, according to the results of this study, serotonin itself behaves more like "sleep factor" than "wake factor".

Since 5-HT containing neurons also secrete glutamate and various neuropeptides, the effect of their destruction may be quite different from that of the elimination of serotonin itself. In the work of Japanese authors [16], carried out using polysomnographic recording, neurotoxic destruction of serotonin-containing DR neurons in special genetically engineered mice led to a decrease in REM sleep at night, when its representation is already low. In addition, according to the data of the same authors, in the experimental mice, in comparison with the control ones, the response to the new environment was weakened and the power of the theta rhythm in wakefulness was increased. However, all these effects were so small that they were detected only with the help of statistical tricks. This, however, did not prevent the authors from concluding that their data support the main hypothesis about the role of serotonin as a factor of wakefulness (positive) and REM sleep (negative), presented above.

Finally, in a recently published study led by renowned Boston somnologist Patrick Fuller using a novel method of highly selective chemogenetic activation of serotonergic neurons in the DRN in combination with polysomnography and behavioral tests, no unambiguous results were obtained either [17]. A "compensatory" restoration of NREM sleep, slightly suppressed by the 5-HT neuron activator injection procedure, was shown to return to baseline levels. This effect can hardly be called somnogenic, but it is definitely not activating. In addition, a change in behavior in the open field was found, which the authors interpret as a decrease in the level of anxiety under the influence of the activation of serotonergic neurons in the DRN.

However, testing in a cruciform elevated maze revealed no changes. The authors refer to a recent study that revealed the existence of two mutually intertwining serotonergic subsystems in the DRN that innervate the orbital frontal cortex and the central amygdala differently. One of these subsystems supports anxiogenic and the other anxiolytic functions. It is possible that the simultaneous activation of both subsystems is associated with the uncertainty of the results obtained in such experiments [17].

As mentioned above, most serotonin-secreting neurons are "silent" during the entire period of REM sleep until the moment of its completion (by awakening or re-entering NREM sleep), and in fact not one single serotonin molecule is released from the presynaptic membrane during this time.

As can be seen from the **Table 1**, the intercellular fluid in wakefulness is saturated mainly with the mediators with depolarizing action on the postsynaptic membrane. During the transition to NREM sleep, all these molecules quickly disappear from the intercellular environment being replaced by the main inhibitory mediator of the brain, GABA, that concentration increases with the deepening of NREM sleep, and the peptide galanin colocolized with GABA. The cerebral biochemical environment in REM sleep is special. High levels of acetylcholine, glutamate and galanin are combined with a complete absence of orexin (hypocretin) and monoamines — serotonin, norepinephrine and histamine, with the exception of dopamine, the concentration of which may sometimes even exceed that in wakefulness. A new mediator appears, the MCH peptide, which mediates the hypothalamo-pontine level of REM sleep regulation. The release of GABA in general is significantly reduced, but remains high in areas of the orexinergic (LHA), histaminergic (TMN), serotonergic (DR) and noradrenergic (LC) neurons localization. In these systems, GABAergic neurons play the role of a "lock" preventing depolarization of these cells during the entire period of REM sleep.

Neurotransmitters	Localization	W	NREM sleep	REM sleep
5-HT	DR	↑↑	↓→↓↓	↔
Norepinephrine	LC	↑↑	↓→↓↓	↔
Histamine	TMN	↑↑	↓→↓↓	↔
Dopamine	VTA/SNpc/vPAG	↑↑	↓	↑
Acetylcholine	LDT/PPT/BF	↑↑	↓→↓↓	↑↑
Glutamate	PC/PB/BF	↑↑	↓→↓↓	↑↑
GABA	Total brain	↑/↓	↑↑	↑/↓
Orexin/Hypocretin	LHA	↑↑	↔	↔
Galanin	VLPO/MnPO	↓	↑↑	↑↑
MCH	LHA/PH	↓	↓	↑↑

Abbreviations: W – wake; NREM sleep – non rapid eye movement sleep; REM sleep - rapid eye movement sleep; 5-HT – serotonin; GABA – γ-aminobutyric acid; MCH – melanin-concentrating hormone; LC – locus coeruleus; DR – dorsal raphe; TMN – tubero-mammillar nucleus; VTA – ventral tegmental area; SNpc – substantia nigra/pars compacta; vPAG – ventral periaquetuctul gray matter; LDT/PPT – latero-dorsal tegmentum/pedunculo-pontine tegmentum; BF – basal forebrain; PC/PB – preceoruleus/parabrachialis nuclei; LHA – lateral hypothalamic area; VLPO – ventro-lateral preoptic area; MnPO – median preoptic area; PH – posterior hypothalamus; ↑ – increase in release; ↓ -decrease in release; ↑↑ - substantial increase in release; ↓↓ - substantial decrease in release; ↑/↓ - increase or decrease in release dependently of the site of cerebral localization; → – gradual decrease in release; ↔ – release ceased.

Table 1.
A simplified scheme for the secretion of cerebral neurotransmitters in the sleep–wake cycle (data from animal studies).

Obviously, the level of serotonin (as well as norepinephrine and histamine) at the sites of projection of aminergic neurons (and, possibly, in the brain as a whole) can decrease during this time. However, the periods of REM sleep in all animals are short, and in some species (small rodents, birds, etc.) they are extremely short (from a few seconds to 1 min) [18, 19]. So this decrease cannot be significant, and in the subsequent period of wakefulness, the normal, "basal" level of serotonergic transmission is quickly restored.

The situation is different in humans. In adults, unlike animals, sleep is of a continuous, so-called "monophasic" or "consolidated" nature. This means that an adult living in modern urban conditions is waking all day (16 hours), and the entire daily "quota" of sleep, usually 5 cycles 1.5 hour each, is realized at night "at a time." In this case, the first half of the night sharply differs from the second - and this is another important difference between human sleep and animal sleep (**Figure 1**, upper graph). In the first half of the night, a person implements mainly the need for deep slow wave sleep (NREM), which has accumulated over a long period of wakefulness (stage 3; according to the old classification - stages 3 + 4, "delta sleep" is apparently a state that is critical for the survival of the organism). In the second half of the night, the need for REM sleep is realized, which alternates with periods of superficial NREM sleep (stage 2). At the same time, individual periods of REM

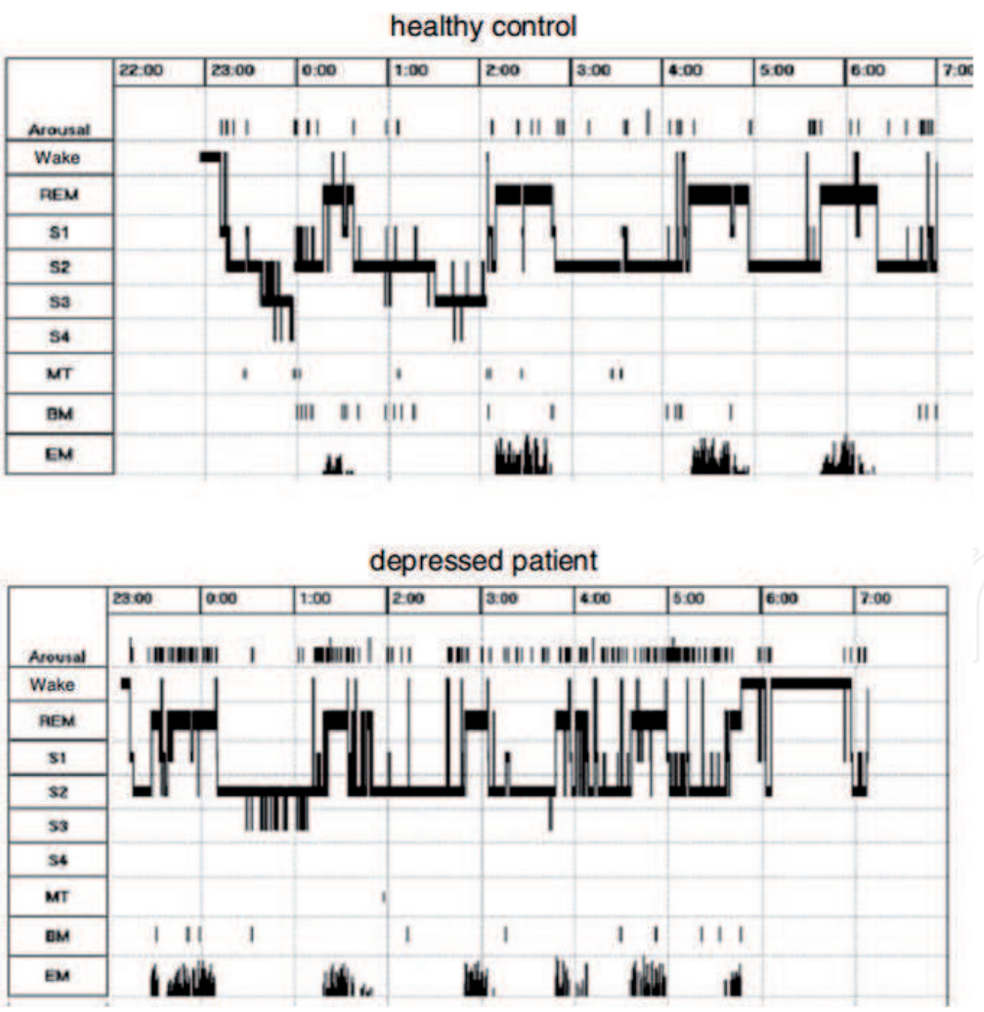

Figure 1.
A hypnogram of a healthy human subject (top) and a depressed patient (bottom) [20]. W - wakefulness, REM - REM sleep, S1-S4 - stages of NREM sleep, MT and BM - various types of movements during sleep, EM - rapid eye movements. It can be seen that the patient has fragmented sleep, REM sleep is disinhibited, and deep NREM sleep (stages 3 and 4; according to the new classification, they combined into one), on the contrary, is suppressed.

sleep, which in a healthy person occupies about 2 night hours, can last 20, 30, and even 40 minutes in the last sleep cycles [20]. Naturally, such long periods of inactivity of the "serotonin factory" of the brain cannot pass without leaving a trace.

What determines these differences in the structure of human sleep? A newborn baby sleeps around the clock with short sucking breaks, total about 16 hours, 8 of which is occupied by the so-called "activated sleep", which is considered as the precursor of adult REM sleep. A one-year-old child has two periods of daytime sleep, and a four-year-old is allowed to sleep only once a day, after lunch. An eight-year-old is already attending school and cannot sleep during the day, and this daily rhythm (without daytime sleep) is maintained by the majority of the modern urban population for life. Psychophysiological studies of the wakefulness-sleep rhythm carried out at one time in healthy subjects who were transferred to a 24-hour bed rest when isolated from the external environment [21], as well as some observations of ethnographers on the nature of sleep in primitive tribes living in isolation from civilization [22], allow to make the following assumption. By nature, a person has a sleep–wake rhythm with two periods of short naps. With this mode, the duration of night sleep is significantly shortened; a person can get up at dawn (in summer). Sleep becomes less consolidated, sleep cycles can be interspersed with more or less prolonged episodes of wakefulness. The differences between the first and second half of the night are smoothed out. In general, human sleep begins to resemble more animal sleep [21–23]. The monophasic nature of sleep of a modern person, apparently, is associated not so much with biological, genetic factors, as with the "pressure of civilization", distorting, disrupting the natural alternation of wakefulness and sleep. During a 16-hour daytime period of continuous wakefulness, a modern person experiences repeated "intrusions" of sleep mechanisms, realized in the form of episodes of local sleep, microsleep and an increase in the delta index in the EEG [24]. A monophasic diurnal rhythm (without daytime sleep) is acquired by the majority of the modern urban population in childhood and retained for the rest of their lives [25].

Thus, the circadian rhythm of a modern urban person is 16 hours of sleep deprivation, followed by 8 hours of sleep. And the law of "rebound" is as follows: first, delta sleep is restored (stage 3), then REM sleep [26]. On the other hand, superficial sleep is considered an "optional" state, which "can be dispensed with." Consequently, the unusually long pre-morning periods of REM sleep, in which serotonergic transmission can be severely depleted, are mainly due to "civilization pressure" disrupting natural circadian dynamics.

3. Serotonin and depression

Although the role of serotonin in the regulation of the wakefulness-sleep cycle remains not completely defined, its participation in emotional reactions is well known. In popular literature, serotonin is often referred to as the "happiness hormone". Excessive activation of serotonergic transmission in the brain causes movement disorders – part of the so-called "serotonin syndrome", and insufficient activation seems associated with diseases such as depression, schizophrenia, anxiety disorders, etc. [27, 28]. In the 50–60s of the last century, the so-called "catecholaminergic" hypothesis became widespread, linking the occurrence of depression with a lack of noradrenergic transmission. It was replaced by the "serotonin" hypothesis of endogenous depression, which was first published in the Lancet magazine in an article by a psychopharmacologist from Leningrad (USSR, now St. Petersburg, Russia) Izyaslav (Slava) Lapin and his graduate student Gregory Oxenkrug: "Intensification of the central serotoninergic processes as a possible

determinant of the thymoleptic effect" [29]. The article had about 350 citations in the first 18 years (to date, according to Google searches, about 800). This led Eugene Garfield to include it in the "This Week's Citation Classic" section of the Current Contents and to publish a note by Oxenkrug on how the article was created [30].

Lapin and Oxenkrug were the first to link emotional disorders and sleep disturbances in depression with a common causative factor - impaired serotonin transmission due to changes in the turnover of cerebral serotonin. Reducing serotonergic transmission in the brain through the hypothalamus-pituitary–adrenal cortex axis disinhibits the release of cortisol. Cortisol activates the enzyme tryptophan dioxygenase (TDO), which "shunts" the normal turnover of serotonin and converts it (in the presence of the pro-inflammatory cytokine γ-interferon, which appears in response to stress) into kynurenine. As a result, serotonin is released less and less. Neuroactive kynurenines, in turn, increase anxiety and impair cognitive performance. Subsequently Lapin showed that the metabolism of kynurenine in the absence of vitamin B6 leads to the appearance of diabetogenic derivatives [31]. The impact of Lapin's ideas on the further development of world psychiatry and psychopharmacology was described in detailed reviews by Oxenkrug [32, 33].

Later, other authors developed a "new serotonin hypothesis" [34], according to which an increased level of glucorticoids, systemic inflammatory processes, and neuroimmune activation of microglia stimulate the synthesis of enzymes tryptophan dioxygenase and indoleamine dioxygenase (TDO/IDO) and finally shift the breakdown of tryptophan to the kynurenine pathway. Finally, the initial development of Lapin recently received a new generalization in the form of the so-called "serotonin-kynurenine-inflammatory" hypothesis of the onset of depression (see **Figure 2**) [35, 36]. Based on the latest biochemical and molecular biology studies, these authors show that the metabolites of kynurenine - oxidized kynurenine, quinolinic acid and the cation NAD+ (nicotinamide-adenine-dinucleotide), which have exito- and neurotoxic properties, cause an excessive increase in glutamatergic neurotransmission, suppressing neurogenesis in the *fascia dentata* of the hippocampus, apoptosis and neurodegeneration. The kynurenine pathway of serotonin metabolism occurs in microglia, and the proliferation of microglia has been found in a number of studies using neuroscanning of depressed patients. So, despite the fact that modern theories of the origin of depression concentrate more on neuroinflammatory and neurodegenerative processes [36–39], Lapin's serotonin idea, put forward more than half a century ago has not lost its relevance.

Back in 1960, a reduced (almost 3 times) level of serotonin in the cerebrospinal fluid of depressed patients was confirmed [40]. And selective serotonin reuptake inhibitors (increasing 5-HT concentration in the synaptic cleft) have been widely and successfully used in clinical medicine as antidepressants for more than 30 years [2]. However, the generalizing works of the last two decades have given some authors the basis for a paradoxical conclusion that not suppression, but, on the contrary, the excess of serotonin neurotransmission is the cause (or at least one of the causes) endogenous depression (melancholy), or that serotonin is not involved at all in the pathogenesis of this disease [41–44].

In recent years, researchers have turned their attention not to cerebral serotonin itself, but to its carrier protein (5-HTT) and the gene for this protein. It turned out that people homo- or heterozygous for its short allele are less resistant to stress and are more at risk of developing insomnia and depression than carriers of the long allele [45]. The short allele is associated with a decrease in the number of 5-HTT binding regions on the surface of the presynaptic membrane and, accordingly, in the reuptake of excess serotonin. From this point of view, the disorder of serotonin transmission in some types of depression, in fact, may be associated more with an excess than a lack of serotonin in the synaptic cleft.

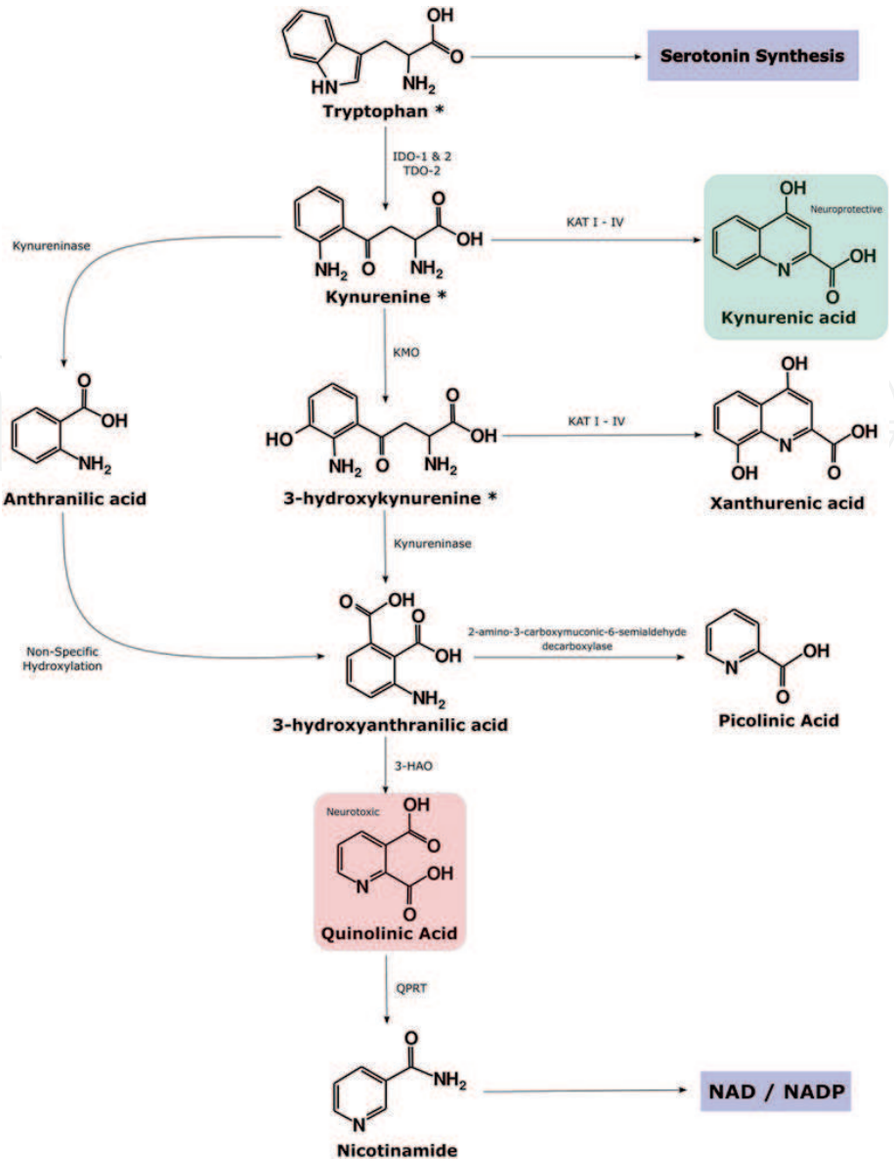

Figure 2.
Simplified illustration of the kynurenine pathway. Tryptophan (TRP) is predominantly converted into kynurenine (KYN) by the indoleamine 2,3-dioxygenase (IDO) isozymes and tryptophan dioxygenase (TDO). IDO-1 is expressed in various immune cells throughout the body, notably dendritic cells, monocytes, and macrophages. Less is known about the more recently discovered IDO-2 enzyme although it is more selectively expressed in dendritic cells, liver, kidney, and the brain and it does not appear to have a significant effect on peripheral kynurenine concentration. TDO-2 is an alternative nomenclature for TDO. KYN can be metabolized into kynurenic acid (KYNA), which is usually considered to be neuroprotective, by the KAT isozymes. Alternatively, it may be converted into anthranilic acid by kynureninase or 3-hydroxykynurenine (3HK) by kynurenine monooxygenase (KMO). Metabolism down the latter pathway increases under inflammatory conditions. 3HK is a free radical generator while quinolinic acid (QA) is a known neurotoxin and gliotoxin. Thus, metabolites in this pathway are usually considered to be neurotoxic. QA is the endogenous source of nicotinamide and nicotinamide adenine dinucleotide (NAD+) [35].

Apparently, under the general term "depression" there is several (and maybe even many) diseases of various etiologies [46]. At the same time, the majority of patients respond positively to the intake of selective serotonin reuptake inhibitors (SSRIs). Moreover, almost any drug that inhibits the reuptake of monoamines (primarily serotonin, but partly also norepinephrine and dopamine) has thymoleptic (antidepressant) properties [46]. However, a very long interval (calculated in weeks) from the start of antidepressant administration to the appearance of a therapeutic effect is an indirect indication that the lack of monoaminergic transmission is most likely a secondary, "downward" consequence of some still unknown primary disorders [46]. Nevertheless, for most cases of endogenous depression

(major depression), the hypothesis of monoamine deficiency is still considered the most acceptable [46]. Apparently, the impairment of serotonergic neurotransmission is one of the links in a cascade of molecular biological events that ultimately lead to neuroinflammatory and neurodegenerative changes in certain parts of the brain, as mentioned above.

The main difficulty faced by this hypothesis is the *reason* for the decrease in serotonin levels in the brain during depression. Among the possible reasons, either an increased activity of the MAO enzyme, which metabolizes serotonin, or a mutation with loss of function of the gene of the Tph-2 enzyme, which synthesizes serotonin, is proposed. In this review, we propose a third reason that can explain a number of cases of "spontaneous" onset of depressive symptoms in apparently healthy people, as well as link the hypotheses of "monoamine deficiency" and "circadian rhythm disturbances" [46].

4. Sleep and depression

Depression is one of those relatively few diseases that are characterized by pronounced and rather specific sleep disorders. In addition, these disorders can occur much earlier than the main symptoms (mood disorders, etc.), and therefore serve as important predictors of the disease. Non-specific disorders in depression include difficulty falling asleep, frequent nighttime awakenings, and early morning awakenings. However, there is a more specific violation of the sleep structure: suppression of deep NREM sleep (stage 3) and disinhibition of REM sleep (see **Figure 1**, lower graph). The suppression of deep SWS manifests itself in the loss of stage 4 (according to the old classification), reduction and fragmentation of stage 3, a decrease in the EEG delta index, and lengthening of stage 2. The disinhibition of REM sleep is manifested both quantitatively and qualitatively. Quantitatively, by reducing the latency of the onset of the first REM period down to zero, when sleep can begin with a REM episode, which never happens in a healthy adult; lengthening the first REM period; an increase in the proportion of the total duration of REM sleep in all night sleep. Qualitatively, the disinhibition of REM sleep manifests itself in an increase in the generation of rapid eye movements already in the first REM sleep period. Although similar disorders of REM sleep are observed not in all patients with depression, but only in 50–70% (according to various sources), and similar phenomena of REM sleep "disinhibition" can sometimes be observed in other neuropsychiatric disorders (schizophrenia, manic psychosis), nevertheless for "major" depression, they are much more typical and more pronounced [37].

As noted above, suppression of neurogenesis in adult animals was shown in various experimental models of depression (mice, rats) [47]. Interestingly, in other models associated with an increase in REM sleep (some forms of stress), according to some data, neurogenesis in the hippocampus is also impaired. On the other hand, inhibition of neurogenesis is also observed in sleep deprivation [37].

One of the main arguments in favor of the hypothesis of a causal relationship (rather than just a correlation) between depression and REM sleep is the effects of antidepressants. It is well known that most antidepressants that prevent the natural breakdown of serotonin (and other brain amines): tricyclic drugs, selective serotonin reuptake inhibitors (SSRI), deeply inhibit REM sleep. Especially effective in this regard are MAO inhibitors, which can almost completely eliminate REM sleep for months and years [37–39]. Millions of patients around the world have taken and are taking these drugs. No cases of cognitive impairment were reported; instead, there is some evidence that MAO inhibitors even improve memory! On the contrary,

the latest generation of benzodiazepines, used as hypnotics and practically do not disturb the duration and distribution of REM sleep, have a pronounced detrimental effect on memory due to the effect of these drugs on the GABA signaling system [48–51].

Now, imagine that in the human population, with its unusually wide gene diversity, there are subjects with initially lowered levels of cerebral serotonin. This may be due to some gene polymorphisms that cause, for example, the synthesis from dietary tryptophan, not serotonin, but kynurenines (as Lapin believed) [29, 31–33]), or a decrease in the formation of tryptophan hydroxylase-2, which synthesizes cerebral serotonin from its precursor, or an increased level of the MAO-A enzyme, which metabolizes serotonin, etc. For such people, long pre-morning periods of REM sleep become especially dangerous, since they can reduce the level of cerebral serotonin below a certain critical level, the threshold for disruption of general serotonergic transmission and the occurrence of emotional disorders. This approach is confirmed by the subjective reports of patients reporting the appearance of the first feelings of depression even during the experience of morning dreams and reaching their maximum severity immediately upon awakening. However, by the evening (as cerebral serotonin accumulates in the course of a vigorous state), the patient's condition gradually improves, depressive symptoms go away by themselves, and he/she feels completely healthy … until a new period of sleep comes! [46]. It is clear that against the background of a low, near-threshold level of cerebral serotonin, even immersions in NREM sleep causing a decrease in serotonin release can re-launch pathological processes in the brain.

On the other hand, the release of cerebral serotonin is involved in the inhibition of the glutamatergic/cholinergic center of REM sleep triggering in the pons [5, 9, 10]. Then, the weakening of this inhibition may be associated with a well-studied increase in the "pressure" of REM sleep in depression, which manifests itself, in particular, in the shortening of the latent period of the first episode of this sleep phase, as mentioned above [37–39]. Moreover, according to some reports, even genetic relatives of such patients, who do not suffer from depression, but, assuringly might have the same gene polymorphism and, as a result, a lowered "basal" level of cerebral serotonin, also have excessively prolonged periods of REM sleep [37]. That is, one can assume that all people who initially have a lowered level of cerebral serotonin, due to this, have an increased "pressure" of REM sleep, which further lowers this level.

It becomes clear why it is not possible to create a more or less adequate experimental model of stress-induced anhedonia (depression) [52]. For this, apparently, it is necessary to adapt the experimental mice to "human conditions": a constant 16-hour sleep deprivation (in the dark period of the day) accompanied by its 8-hour "return" (in the light period). And it is necessary to influence chronic stress also in the dark period against the background of this artificial circadian rhythm. It is possible that in this case the applied impacts will be more effective.

5. Conclusion

Thus, according to the proposed hypothesis, the formation of depression is due to a combination of two factors - a reduced level of cerebral serotonin and the structure of human night sleep with extremely long pre-morning periods of REM sleep. It is known that total sleep deprivation (or selective REM sleep deprivation) is used as an effective but short-term thymoleptic action. According to the proposed approach, fragmentation of REM sleep can be just as effective. If it really turns out

to be effective in alleviating depressive symptoms, then it can be relatively easily automated by giving the patient during REM sleep signals (for example, sound), selected so that they do not wake him up at all, but only wake him up, transferring from REM sleep to the 2nd or 1st stage of NREM sleep. Such a procedure, which is much more easily tolerated by patients, will also be suitable for chronic use.

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