Psychiatr. Pol. 2025; 59(5): 707–720
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/205845

Sixty years of neurotransmitter concepts of mood disorders

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Summary

The year 2025 marks the sixtieth anniversary of the publications that first proposed the neurotransmitter hypothesis of the pathogenesis and treatment of affective disorders. This concept, assuming the dominant function of catecholamines (noradrenaline and dopamine), further added with serotonin, is probably the most important theory regarding the biological pathogenesis and psychopharmacology of affective disorders. A history of the discovery of these neurotransmitters and their role in the central nervous system is presented.

The catecholamine hypothesis was proposed in 1965 by American researchers Joseph Schildkraut, William Bunney and John Davis. It concerned a deficiency of noradrenaline in depression and its excess in mania, and later, a similar role of dopamine. The serotonin hypothesis of depression was presented in 1969 by the Briton Alec Coppen and the Soviet researchers Izaslaw Lapin and Grigorij Oxenkrug.

The neurotransmitter concepts, especially serotonin theory, contributed to the discovery and introduction of new antidepressants. The selective serotonin reuptake inhibitors have become the most frequently used antidepressants nowadays. The introduction of fluoxetine (Prozac) in the USA at the turn of 1980s/1990s was a cultural event. In the 21st century, serotonin has made a career as a hormone of happiness and has appeared in literary works.

Also now, the interpretation of the mechanism of action of the majority of antidepressants concerns their enhancement of noradrenergic, dopaminergic and serotonergic transmission in the central nervous system. The therapeutic effect in mania is associated with an inhibition of dopaminergic transmission. Among other neurotransmitters, acetylcholine can be mentioned as an element of the cholinergic-adrenergic hypothesis of mood disorders. Whereas the introduction of ketamine pointed to the role of glutamatergic neurotransmission in the pathogenesis of depression.

Key words: mood disorders, catecholamines, serotonin

Introduction

This year, we observe a sixtieth anniversary of the publications, which proposed, for the first time, a neurotransmitter hypothesis of the pathogenesis of mood disorders

and the mechanism of action of antidepressant drugs. This concept assumes a fundamental role in some substances transmitting signals between neurons on the synapses. Concerning such neurotransmitters as catecholamines, a deficiency of noradrenaline was postulated in depression and its excess in mania, which was further supplemented by a similar role of dopamine. In 1969, the neurotransmitter concepts were extended by the significance of serotonin in the pathogenesis of depression and the mechanism of action of antidepressant drugs. The neurotransmitter hypothesis made the first consistent attempt to elucidate the pathogenesis and psychopharmacology of mood disorders on the neurobiological level. Along with parallel development of the dopaminergic concept of the pathogenesis of schizophrenia and the mechanism of action of antipsychotic drugs, biological psychiatry and psycho-pharmacology became predominantly "neurotransmitter-based" in the following decades.

Through many decades, neurotransmitter theories monopolized the views and research on the pathogenesis of mood disorders and the mechanisms of drug action in these illnesses. It was fostered by the fact that they could explain the different aspects of the action of the antidepressant drugs in an understandable, although a little mechanistic way. Besides, even in the 21st century, taking into account the new data on catecholamines and serotonin as well as the role of these neurotransmitters' transporters and numerous receptors, the action of most antidepressant and antimanic drugs, as well as many symptoms of affective diseases, can be interpreted in such a way. Whereas, among various neurotransmitters associated with depression, it was serotonin that launched the greatest career.

In this article, a history and current status of the neurotransmitter concepts of mood disorders will be presented. A gallery of researchers who played the greatest role in their development will be shown as well as small personal digressions will be added.

Noradrenaline, dopamine, and serotonin

Chronologically, the identification of catecholamines (adrenaline, noradrenaline, and dopamine) as the substances significant for mental functions proceeded in an inverse sequence as their position in the synthesis pathway. The end product of catecholamine synthesis is adrenaline. Adrenaline is a hormone secreted by the adrenal medulla which plays a crucial role in stress reaction. It is named the 3F hormone – fright, fight, and flight. Whereas its function as a neurotransmitter in the central nervous system (CNS) is slight. In the discovery of adrenaline at the turn of the 19th and 20th centuries, a prominent contribution was made by a Polish physiologist, Napoleon Cybulski (1854–1919) [1]. He isolated this substance from the adrenal gland and gave it the Polish name "nadnerczyna" ("nadnercza" – in Polish means "adrenal glands"). Etymologically, it relates to the name "epinephrine" proposed in 1897 by an American researcher, John Abel, which comes from Greek (*epi* – above, *nephros* – kidney) [2] and the name "adrenaline", coming from Latin (*ad* – above, *ren* – kidney), introduced in 1901 by a Japanese researcher, Jōkichi Takamine [3]. In acknowledgement of his achievements, Napoleon Cybulski was nominated three times for the Nobel Prize in

Physiology and medicine (in 1911, 1914, and 1918), however, unlike the discoverers of noradrenaline and dopamine, which will be mentioned later, he never received it.

As a substance playing a significant role in mental processes, the adrenaline made in 21st century an everyday colloquialism. A person striving to constantly experience strong stimuli is called "dependent on adrenaline." It is also said that "life is boring without adrenaline."

Noradrenaline is a precursor of adrenaline. In 1946, a Swedish researcher, Ulf von Euler (1905–1983), working at the Karolinska Institutet in Stockholm, demonstrated that noradrenaline serves as a transmitter in the sympathetic nervous system [4]. For his research on neurotransmitters, von Euler received the Nobel Prize in 1970. In the 1970s, the locus coeruleus, a nucleus in the pons of the brainstem, was identified as a main source of noradrenergic neurons in the CNS [4].

Then, dopamine is a precursor of noradrenaline. As the main researcher responsible for the identification and analysis of its action, a Swedish psychopharmacologist from Gothenburg, Arvid Carlsson (1923–2018) can be regarded. In 1957, Carlsson demonstrated that dopamine serves in CNS as an independent neurotransmitter, and not only a precursor of noradrenaline as was then thought [6]. Whereas his paper from 1963 indicated a possible role of dopamine in the mechanism of action of antipsychotic drugs [7]. On the sixtieth anniversary of the event, the article dedicated to this appeared in *Pharmacotherapy in Psychiatry and Neurology* [8]. The further studies on dopaminergic system carried out by Carlsson resulted in theories of dopamine deficiency in Parkinson's disease and dopaminergic hyperactivity as a main cause of psychotic disorders and an essential element of the pathogenesis of schizophrenia. These concepts translated into a therapy – using the precursor of dopamine, L-dopa, in Parkinson's disease, and the application of neuroleptic (antipsychotic) drugs which, as transpired later, block dopaminergic receptors, in the treatment of schizophrenia [9, 10]. For his research on dopamine, Carlsson received the Nobel Prize in 2000.

Initial studies on serotonin pertained to its role in the gastrointestinal system. An Italian investigator, Vittorio Erspamer (1909–1999) showed in 1937 that a substance named by him enteramine caused smooth muscle contraction, among others, in intestines [11]. For his achievements, Erspamer was nominated twice for the Nobel Prize. The name "serotonin" was introduced in the late 1940s by American researchers as a substance released from platelets and causing a vascular contraction (Latin *serum* – serum, Greek *tonikos* – strengthen) [12]. The name has been functioning alongside the international term "5-hydroxytryptamine." Whereas the action of serotonin as a neurotransmitter was for the first time shown in 1954 by an American researcher, Betty Twarog (1927–2013) [13]. In the 1970s, the dorsal raphe nuclei were identified as a main source of serotonergic neurons in the CNS and their relationship with serotonergic activity [14]. In this research a significant contribution was made by Polish psychopharmacologists, directed by an eminent scientist, Wojciech Kostowski (1939–2023) [15].

The first concept on the pathogenic role of the serotonergic system in psychiatric disorders was proposed by an American biochemist, Dilworth Woolley (1914–1966). He showed that a psychedelic substance, diethylamide of lysergic acid (LSD), caused

changes in the serotonergic system [16]. In 1963, he published a book *The Biochemical Bases of Psychoses or the Serotonin Hypothesis about Mental Illness*, in which he postulated that psychiatric disorders are brought forth by exogenous or endogenous substances antagonistic to serotonin [17]. For his research on serotonin and vitamins, Wolley was many times nominated for Nobel Prize (in 1939, 1948, 1949, and 1950).

Noradrenergic concept of mood disorders

American researchers, such as Joseph Schildkraut (1934–2006) and William Bunney (born in 1930), working in the National Institute of Mental Health (NIMH) in Bethesda can be considered architects of the catecholamine theory of mood disorders. Joseph Schildkraut graduated from Harvard University, and shortly then spent several years in NIMH researching on mood disorders. In his 1965 article, he pointed to such pharmacological data as an augmentation of noradrenergic transmission by antidepressant drugs such as imipramine and monoamine oxidase inhibitors. Therefore, he postulated a deficit of noradrenaline in depression and its excess in mania [18]. In the late 1960s, Schildkraut returned to Boston and worked in the Massachusetts Mental Health Center. He continued his studies on the role of the noradrenergic system in mental disorders, the association between depression, creativity, and mood disorders in eminent artists. The result of the latter was an edited book [19]. As a representative of psychiatric neurobiology, he was an exception, because Harvard psychiatry was dominated then by psychoanalysis.

In the same year, William (Bill) Bunney together with John Davis (1928–2024) from Chicago published a paper in which, based on the effects of imipramine, MAOI, and reserpine, they suggested a significant role of noradrenaline in the etiopathogenesis of depression and the mechanism of action of antidepressant drugs [20]. Bunney worked many following years in NIMH and was regarded as the most eminent researcher of the neurobiology of mood disorders in the USA. When I was in America in 1977, receiving the National Institutes of Health's fellowship, Bunney arranged for me a visit to the NIMH, where I had an opportunity to acquaint his numerous excellent colleagues such as, e.g., Robert Post, Daniel van Kammen or Monte Buchsbaum, who have played a significant role for biological psychiatry in America. For many years now, William Bunney has been a professor of psychiatry at the Irvine School of Medicine, University of California. Whereas John Davis until the end of his life worked in the University of Illinois in Chicago. In the 1970s, he became famous as the author of the first meta-analyzes in psychiatry on the efficacy of long-term pharmacological treatment in schizophrenia and mood disorders [21, 22].

A significant contribution into the noradrenergic concept of depression became a hypothesis of the down-regulation of noradrenergic receptors caused by antidepressant drugs, as a therapeutic mechanism in depression. The hypothesis was proposed in 1975 by the eminent Polish psychopharmacologist, Jerzy Vetulani (1936–2017) working then at the Vanderbilt University in Nashville, together with Fridolin Sulser. Such a phenomenon could explain some "delay" in the action of antidepressant drugs [23].

The noradrenergic concept of depression pathogenesis has been reflected in the pharmacological profile of some antidepressant drugs. In the mechanism of action of desipramine, a tricyclic antidepressant introduced in 1964, the most important is an inhibition of synaptic reuptake of noradrenaline. In 1974, a tetracyclic antidepressant, maprotiline, was initiated, also having a preferential effect on noradrenaline reuptake inhibition. The most recent addition, since 1997, is reboxetine, a selective inhibitor of noradrenaline reuptake which, unlike the previous drugs, is not acting on other neurotransmitters.

Dopaminergic concept of mood disorders

In 1975, William Bunney made an update of the catecholamine theory of mood disorders by adding to noradrenaline its precursor, dopamine, which was then flourishing as a brain neurotransmitter [24]. The bipolar dopaminergic concept of mood disorders presumes a deficient dopaminergic neurotransmission in depression and dopaminergic hyperactivity in mania.

The dopaminergic theory of depression as a state of dopaminergic deficit in the mesolimbic system was most fully presented in 2004 by French researchers. They pointed to the data in this respect coming from both studies on animal models and clinical investigations [25]. Whereas the most recent version of the bipolar dopaminergic hypothesis of bipolar disorders (BD) was put in 2017. According to this concept, there is increased activity of striatal dopaminergic D2 and D3 receptors in mania, while in depression, there is increased activity of striatal dopamine transporter, resulting in an attenuation of dopaminergic activity [26].

In the pharmacological context, the dopaminergic concept of depression was confirmed by therapeutic efficacy of bupropion, an antidepressant drug inhibiting the dopamine transporter, introduced in 1985 [27]. Whereas, since the 1950s, it has been known that antipsychotic drugs which block dopaminergic receptors D2, act therapeutically in mania [28]. It is also pointed out that the classic antimanic drug such as lithium, inhibits the synthesis of dopamine in the brain [29].

Serotonergic concept of depression

The serotonergic theory postulates a serotonin deficit in depression, without a reference to manic states. Its originators were British psychiatrist – Alec Coppen (1923–2019) and Soviet researchers Izaslaw Lapin (1930–2012) and Grigori Oxenkrug (born in 1940). The fundamental articles, both of Coppen and the Soviet authors were published in 1969 [30, 31].

Alec Coppen was one of the most prominent representatives of European biological psychiatry of mood disorders, working mainly in the Neuropsychiatric Research Unit in Epsom, Surrey. In his article of 1969, he postulated a deficit of the serotonergic system in depression [30]. He was also a promotor and researcher of many other pathogenic and therapeutic concepts of mood disorders, among others, disturbances of neurotransmitters, water and electrolytes disturbances, and metabolic changes.

He became a great supporter of lithium administration and is regarded as the first who demonstrated anti-suicidal action of this ion [32]. In 2000, Coppen received the Pioneers in Psychopharmacology Award by the Collegium Internationale Neuro-Psychopharmacologicum.

Both Soviet researchers, whose article published in the *Lancet* can be regarded as a pioneering for the role of serotonin in the pathogenesis of depression, worked at the Bechterev Psychoneurological Institute in Leningrad. Wladimir Bechterev (1857–1927) who established this institute in 1907, was an eminent Russian neurologist, psychiatrist, and researcher of brain function. On 22 December 1927, he was summoned for consultation with Joseph Stalin on account of some hand paresis of the Soviet leader. After the examination, he told to his assistant Samuil Mnuchin waiting in the corridor that Stalin had symptoms of severe paranoia and that a dangerous man was ruling the country. On 23 December, Bechterev was chairing the Neurological Congress in Moscow, and after the afternoon session, he went to the theatre with his wife. During the interval, he was invited by two young men, probably working for the political police (OGPU) for cake and something to drink. When returned home, he felt very bad, and the next day passed away.

Izaslaw (Slawa) Petrovich Lapin can be regarded as a creator of Russian experimental psychopharmacology. In the article of 1969, he proposed that a therapeutic action of antidepressant drugs is associated with an augmentation of serotonergic neurotransmission, which is lowered in depression. He also suggested that the serotonin deficiency in depression might result from shifting tryptophan metabolism from the "serotonin" to "kynurenine" pathway [31]. Thus, he may be an author of the "kynurenine" theory of depression pathogenesis. Besides having characteristics of a prominent researcher, Lapin was a man of multiple talents (music, painting) and a friend of Soviet dissidents, Elena Bonner and Andrei Sakharov. When meeting him at scientific conferences I was impressed by his excellent knowledge of the Polish language.

The co-author of the article from 1969, Grigori Oxenkrug, emigrated to the USA in the 1980s. He continued psychopharmacological and neurobiological research, also on the kynurenine theory of depression. In recent years, he has worked as a professor of psychiatry and a head of the *Psychiatry and Inflammation* program at the Tufts University in Boston.

The influence of the serotonergic concept on the development of new antidepressants

The neurotransmitter concepts of depression, especially the serotonin one, contributed to the discovery and introduction of new antidepressant drugs. In the early 1980s, serotonergic antidepressant drugs – selective serotonin reuptake inhibitors (SSRI) were inaugurated. Their homeland was Sweden due to the involvement in the project of the already mentioned great psychopharmacologist from Gothenburg, Arvid Carlsson. However, the first drug of this group, zimelidine, was shortly withdrawn on account of the cases of Guillain-Barré syndrome reported in the course of its administration [33]. Whereas fluvoxamine, initiated in 1984, has been successfully used until now [34].

The late 1980s brought about an initiation of the SSRI drug, fluoxetine, known commercially as Prozac, in the USA. This fact can be defined as a cultural event in this country. The particular feature of fluoxetine was its spectacular therapeutic effect in mild depression, previously qualified for psychotherapeutic treatment. While the psychotherapy was sometimes effective after several months, the fluoxetine-induced improvement was pretty rapid. This caused a significant paradigm shift in the perception of depression as having a *par excellence* biological foundation and thus a possibility of pharmacological treatment. For all that, some Americans still believe that "real" psychopharmacology started only after Prozac was introduced.

In 1993, an American psychiatrist, Peter Kramer, published a book *Listening to Prozac*, in which he included a whole range of interesting observations. One of them concerned the possibility to achieve during fluoxetine therapy desired personality changes often required significantly longer psychotherapeutic treatment. However, he expressed his concern over whether Prozac might initiate a field of so-called cosmetic psychopharmacology associated with the modification of psychopathological symptoms of minimal severity [35]. In 1995, the book was published in Poland as *Wsłuchując się w Prozac. Przełom w psychofarmakoterapii depresj* [36].

In 1996, an American writer, Elizabeth Lee (Lizzie) Wurzel, wrote a book *Prozac nation*, a confessional memoir of her depression treated with Prozac, also in the context of her writing activity [37]. In 2001, a film with the same title was made based on the book. In Poland, the film was named *Pokolenie P* (*The generation P*).

At the turn of 1990/2000, books written by psychiatrists with a skeptical attitude appeared such as *Talking back to Prozac* [36] and *Beyond Prozac* [38]. In the first one, the drawbacks of fluoxetine are discussed, while the second considers the possibility of improving the serotonin system, not necessarily by using this drug. The book *Prozac backlash. Overcoming the dangers of Prozac, Zoloft, Paxil, and other antidepressants with safe, effective alternatives*, criticizes the use of SSRI drugs and highlights the dangers associated with them [39]. Finally, the publication *Better than Prozac* discusses a new generation of psychotropic drugs, elaborated by taking into account the achievements of neurobiology and molecular genetics [40].

Apart from already mentioned fluvoxamine and fluoxetine, three SSRI drugs (sertraline, paroxetine, citalopram) were introduced in the first part of the 1990s, while escitalopram – in 2001.

Antidepressant drugs of the SSRI group

The SSRI drugs have been the most frequently used antidepressants. Besides depression, they have been widely applied in various anxiety disorders such as obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder, and general anxiety disorder. The pharmacotherapy of OCD received probably the greatest therapeutic support associated with these drugs. Two decades earlier, at the turn of the 1960s/1970s, Spanish researchers initiated in the use of clomipramine, the tricyclic antidepressant having a predominant effect on the serotonin reuptake, in OCD [42]. This research was led by Juan José López-Ibor Aliño (1941–2015), the later President

of the World Psychiatric Association (1999–2002). Before the introduction of SSRIs, clomipramine remained the only medication with confirmed therapeutic efficacy in OCD. Currently, the SSRIs are regarded as drugs of the first choice in OCD, they are used in higher doses than in depression and the therapeutic effect is observed after a longer time [43]. Also in other anxiety disorders such as general anxiety disorder, panic disorder, or social anxiety disorder, the SSRI drugs are the first-line pharmacotherapy in all recommendations.

A common feature of all SSRI drugs is an inhibition of serotonin reuptake (serotonin transporter) and augmentation of serotonergic neurotransmission. However, there are significant differences between them as to the pharmacokinetic properties and effects on other neurotransmitters and receptors. Thus, the attempts of their application in other conditions, beyond depression and anxiety disorders were made. An example can be the use of fluoxetine in eating disorders [44]. Also, during the COVID-19 pandemic, a favorable action of fluvoxamine on the course of infection was observed which was probably related to the effect of the drug on sigma receptors [45].

An important reason for the popularity of the SSRI drugs was significantly fewer side effects compared with tricyclic antidepressants which had been formerly most commonly used. However, two kinds of symptoms deserve special attention. The introduction of the SSRI drugs resulted in a significant increase in interest in a possibility of negative influence on sexual functions as these dysfunctions can be due to inhibitory action of most serotonergic receptors. The sexual dysfunctions are frequent with SSRI use, the most intense with fluoxetine and paroxetine [46]. Moreover, the SSRI drugs may cause a feeling of some psychological "distance" from the environment which can be advantageous in anxiety disorders. However, in recent years it was pointed out that in some patients such a phenomenon is excessive, which may result in a feeling of emotional "blunting" [47]. British investigators showed, using a survey, that emotional blunting may occur in nearly half of patients receiving different antidepressant drugs and pointed out a possible relationship with depression itself [48]

Serotonergic component in the mechanisms of antidepressant drugs

A serotonergic component is important in the mechanism of action of many antidepressant drugs introduced in the 1980s, 1990s, and 21st century. Among drugs initiated in the early 1980s, trazodone can be mentioned as the serotonin antagonist and reuptake inhibitor (SARI) drug. Whereas amidst drugs used from the late 1980s, moclobemide can be listed as the reversible inhibitor of monoamine oxidase type A (RIMA). In the case of the latter, it involves inhibiting the enzymatic degradation of both serotonin and catecholamines, noradrenaline and dopamine.

In the mid-1990s, "dual" action antidepressants were introduced such as venlafaxine and mirtazapine, similar to tricyclic antidepressants influencing both the serotonin and noradrenergic systems. Venlafaxine initiated a group of serotonin and norepinephrine reuptake inhibitors (SNRI) and has become one of the most frequently used antidepressants. In the 21st century, duloxetine was added and promoted for also having a potential analgesic effect. Mirtazapine is defined as the NaSSA (noradrenergic

and specific serotonergic antidepressant). As to the serotonergic system, mirtazapine inhibits 5-HT2 and 5-HT3 receptors having antidepressant action without negative effects on sexual functions.

Other antidepressant drugs introduced in the 21st century include agomelatine (2009) and vortioxetine (2013). The first is a derivative of melatonin, acting on melatonergic receptors M1 and M2, whereas its antidepressant effect is probably due to an additional effect on serotonergic 5-HT2 receptors. Because of its relationship to melatonin, agomelatine is regarded as an antidepressant, additionally regulating biological rhythms and sleep. Vortioxetine is a multi-receptor drug, besides SSRI action, being a partial agonist of serotonin 5-HT1A and 5-HT1B receptors and an antagonist of 5-HT3, 5-HT1D, and 5-HT7 receptors. Such a profile could be associated with a beneficial effect of the drug on cognitive functions.

Serotonin career and controversies

The popularity of the SSRI and SNRI drugs as well as information on the role of serotonin in their mechanism of action, implicating a deficit of serotonin in depression, resulted in the naming serotonin "a hormone of happiness." The term has gradually become fashionable in everyday colloquialism. Although, it reached its climax in the novel of the eminent French writer, the Legion of Honor awardee, Michel Houllebecq, titled *Sérotonine*, published in 2019 [49]. The protagonist of the book is 46 years old Florent-Claude Labrouste taking for his depression medication Captorix (the name invented by the author) which increases the production of serotonin. The drug makes moderately normal functioning possible, however, it produces adverse sexual effects, which is in accordance with the profile of side effects observed with serotonergic drugs. The Polish version of the book has been available since 2023 [50].

However, not a long time ago, the great media stir was caused by the article of the group led by a British psychiatrist, Joanna Moncrieff, published online in July 2022 in a prestigious journal *Molecular Psychiatry*. The authors indicated that there is no evidence for a significant role of serotonin in the pathogenesis of depression, as well as for the efficacy of serotonergic drugs in depression [51]. Shortly after this, in the web portal Wirtualna Polska it was proclaimed that breakthrough study disproved the serotonin theory of depression and its treatment with serotonergic drugs. In response on behalf of the Polish Psychiatric Association, it was pointed out that the so-called serotonin theory of depression was only an element in the development of knowledge on the pathogenesis of mental disorders, and a direct relationship of depression with a low serotonin level makes an unacceptable oversimplification. Whereas the therapeutic action of serotonergic antidepressants has been experienced by millions of patients. The antidepressant effect is due, among others, to the influence on the neuroplasticity of the brain, stress tolerance, and processing of negative stimuli, and the serotonergic system is involved in only some of them. There is no reason to undermine the efficacy and safety of antidepressant drugs, including SSRIs, because they have been confirmed both by many studies and clinical practice. The article provoked a heated discussion in the scientific literature. Perhaps the most accurate riposte was presented by Hungar-

ian authors, discussing pathogenesis of depression in the context of both serotonin as well as catecholamines (noradrenaline and dopamine), and using the drugs acting on all these neurotransmitters [52].

In recent years, the issue of serotonin in depression and its treatment gained a new aspect in the context of studies on therapeutic action in depression of psychedelic drugs, mainly psilocybin [53]. Psilocybin is a serotonin agonist, with special affinity to the 5-HT2A receptors [54]. This can refer back to the concept of the pathogenic role of serotonin antagonists in mental disorders proposed in the 1960s by Dilworth Woolley [17].

Other neurotransmitters

Among other neurotransmitters associated with the pathogenesis of mood disorders, acetylcholine should be mentioned. A hypothesis of adrenergic-cholinergic balance of BD was presented in 1972. Its author was David Janowsky, working at this time in Nashville, and then relocated to the University of California in San Diego [55]. The concept assumed that in depression, there is a dominance of cholinergic neurotransmission, while in mania – the noradrenergic one. The reasoning was mainly pharmacological – reserpine which causes depression exerts cholinomimetic action, while tricyclic antidepressants have anticholinergic effects. In 2015, in a recapitulation of this hypothesis, additional arguments were given such as, e.g., antidepressant effect of scopolamine, the anticholinergic substance [56]. Whereas in Polish studies, it was found that the anticholinergic effect plays a role in a "switch" process, i.e., a change of depressive episode into a (hypo)manic one [57, 58].

In the 21st century, the pathogenic role of glutamatergic neurotransmission in depression has drawn attention due to an antidepressant effect of ketamine, the substance used in anesthesia and for recreational purposes. Ketamine is an antagonist of the NMDA glutamatergic receptor. In a paper of 2006, in a double-blind placebo-controlled trial, it was found that a single ketamine infusion, 0.5 mg/kg, resulted in a rapid improvement and sometimes a remission of depression [59]. The beneficial effects of ketamine infusion as an add-on to mood-stabilizing drugs were also observed in patients with depression in the course of BD [60]. In some studies, it was also found that a ketamine infusion resulted in a rapid disappearance of suicidal tendencies. In recent years, an intranasal ketamine was elaborated, and its efficacy for the augmentation of antidepressant drugs in treatment-resistant depression was demonstrated [61].

Recapitulation

On the sixtieth anniversary of the noradrenergic concepts of mood disorder, after 56 years from the serotonin theory of depression, and 50 years from the dopaminergic concept of mood disorders, it could be acknowledged that these theories have settled down well both in biological psychiatry and psychopharmacology. In recent decades, significant progress in studies on the pathogenesis of mood disorders has been made. It was pointed out that the role, among others, of immunological processes, neuro-

plasticity, stress reaction, as well as the significance of other neurotransmitters was demonstrated. Still, however, an interpretation of the symptoms of depression and mania as well as an action profile of the majority of antidepressant and antimanic drugs can successfully be made in the context of noradrenergic, dopaminergic, and serotonergic neurotransmission. This can make an example of how the development of knowledge on a few substances which are crucial to information processing on the CNS synapses resulted in a cogent concept of the pathogenesis and treatment of mood disorders.

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