Modern Concept of Depression Pathogenesis: The Contribution of I.P. Lapin's Research Team

Вклад работ коллектива И.П. Лапина в становление современной модели патогенеза депрессивных расстройств

doi: 10.17816/CP15601

Information

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ABSTRACT

BACKGROUND: The advent of neuroleptics and antidepressant therapy marked a significant step forward in clinical psychiatry. Numerous experiments worldwide had been dedicated to a search for the potential neurobiological mechanisms underlying the potency of new psychopharmacological drugs. The first laboratory of psychopharmacology in the USSR was established in 1960 at the Leningrad Psychoneurological Institute. It was headed by Professor Izyaslav Petrovich Lapin. The foundational article by Lapin I.P. and Oksenkrug G.F. (The Lancet, 1969) continues to be cited 55 years after its publication, which determines the interest in the role of this research team in shaping temporal concepts of the pathogenesis of depression and the development of psychopharmacology.

AIM: To analyze the contribution of Lapin I.P. and his research team to the development of experimental approaches for studying the mechanisms of depression.

METHODS: We analyzed the articles and monographs authored by Professor Lapin I.P., both individually and in co-authorship, available in PubMed, Google Scholar, eLIBRARY.RU, and in the bibliographic collection of the V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology.

RESULTS: This analysis highlights the significance of Lapin I.P. and his scientific team's work in advancing our understanding of serotonin role in the mechanisms of depression and in the development of animal depression models. The scientific contribution of this team is an important milestone towards future research into the neurobiological mechanisms underlying depression, as well as the development of therapeutic approaches.

CONCLUSION: Lapin's scientific publications and the work of his team in the field of psychopharmacology have had a significant impact on the development of neuroscience and continue to be of unquestionable importance in advancing scientific practice more than 50 years later.

АННОТАЦИЯ

ВВЕДЕНИЕ: Появление нейролептиков и антидепрессивной терапии стало существенным шагом вперед в развитии клинической психиатрии. Поиску возможных нейробиологических механизмов, лежащих в основе действия новых психофармакологических препаратов, были посвящены многочисленные эксперименты во всем мире. В 1960 г. в Ленинградском психоневрологическом институте была создана первая в СССР лаборатория психофармакологии, которую возглавил профессор Изяслав Петрович Лапин. Фундаментальную статью И.П. Лапина и Г.Ф. Оксенкруга (The Lancet, 1969) продолжают цитировать спустя 55 лет после публикации, что определяет интерес к роли этого научного коллектива в формировании временных представлений о патогенезе депрессии и развитии психофармакологии.

ЦЕЛЬ: Проанализировать вклад И.П. Лапина и его научного коллектива в разработку экспериментальных подходов к исследованию механизмов развития депрессии.

МЕТОДЫ: Авторы проанализировали статьи и монографии, написанные профессором И.П. Лапиным как индивидуально, так и в соавторстве, доступные в базах данных PubMed, Google Scholar, eLIBRARY.RU и в библиографическом фонде ФГБУ «Национальный медицинский исследовательский центр психиатрии и неврологии им. В.М. Бехтерева» Минздрава России.

РЕЗУЛЬТАТЫ: Проведенный анализ подчеркивает значимость работы И.П. Лапина и его коллег в углублении понимания роли серотонина в механизмах депрессии и в разработке моделей депрессии на животных. Научное наследие этого коллектива является важной вехой на пути к будущим исследованиям нейробиологических механизмов, лежащих в основе депрессии, а также разработке терапевтических подходов.

ЗАКЛЮЧЕНИЕ: Научные публикации И.П. Лапина и работа его коллектива в области психофармакологии оказали существенное влияние на развитие нейронауки и сохраняют свою значимость для передовых научных исследований уже более 50 лет.

Keywords: *psychopharmacology; affective disorder; neuroscience; history of medicine; history of psychiatry*
Ключевые слова: *психофармакология; аффективное расстройство; нейронаука; история медицины; история психиатрии*

INTRODUCTION

Psychopharmacology, as a branch of clinical pharmacology, underwent intensive development in the middle of the 20th century. However, the deliberate use of pharmacological agents for their psychotropic properties in medicine had begun as early as the 9th century [1]. However, the treatment of pain and insomnia, as well as the psychostimulant effects of certain medicinal products, primarily centered on symptomatic relief and only rarely relied on the understanding of the etiology and pathogenesis of the disorders that held sway at the time [2].

The emergence of psychopharmacotherapy, with effects not only at the symptomatic but also at the syndromal level, enabling the control of psychoses and depressive syndromes, marked a new era in clinical psychiatry. Since the confirmation of the specific psychotropic effects of chlorpromazine, iproniazid, and imipramine, antipsychotics (neuroleptics) and antidepressants (thymoleptics) have been the subject of ongoing research [3, 4]. Neurobiological hypotheses that proposed mechanisms that explained the observed effects of medicinal products and received empirical confirmation subsequently became the basis for the development of new psychotropic drugs [2, 4].

As early as 1960, just 8 years after the publication of the first data on chlorpromazine's efficacy, the first psychopharmacology laboratory in the Soviet Union was established at Leningrad Psychoneurological Institute (currently known as V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology). The novelty of the scientific field and the prompt establishment of this new unit ensured the pioneering nature of the work conducted by the laboratory staff.

In the 1960s, the concept of the leading role of norepinephrine in the development of depression was widely accepted [5]. Studies that allowed for the formulation of the catecholamine hypothesis of mood disorders were largely based on testing the serendipitously discovered psychotropic effects of various pharmacological agents in animal models of depression [6]. One of the first thymoleptics (trazodone), developed in the early 1970s with a predetermined spectrum of neurobiochemical activity, was supposed to lower the pain threshold in depression by acting on α-adrenergic receptors, according to the original hypothesis [7]. However, in 1981, by the time of the drug's approval by the Food and Drug Administration (FDA), its antidepressant effect had become associated with the mechanism of serotonin reuptake. In 1971, another group of researchers was developing a selective serotonin reuptake inhibitor, which was authorized by the FDA in 1988 as fluoxetine [8]. Thus, in the early 1970s, the consensus on the mechanisms of depression development had shifted from the noradrenergic theory to the serotonergic theory. This opened the next stage in the development of psychopharmacology — the targeted synthesis of drugs with the desired properties. Selective serotonin reuptake inhibitors (SSRIs), antidepressants of the currently most common group, appeared. This paradigm shift in the development of psychopharmacology was, to some degree, facilitated by the original research performed by a team at the Psychopharmacology Laboratory of the Leningrad Psychoneurological Institute [9]. It was also supported by their analysis of similar studies by international colleagues (including joint projects with the University of Tartu), focusing on the mechanisms of action of psychotropic agents.

A significant milestone in the field of psychopharmacology was the publication of an article by Soviet scientists Lapin I.P. and Oksenkrug G.F. in the "Hypothesis" section of The Lancet journal in 1969 [10]. Given its scientific importance and high citation count in international scientific literature, Oksenkrug's commentary on the writing of the 1969 landmark article was published in 1987 in the "This Week's Citation Classic" section of "Current Contents" [11, 12]. Lapin I.P. and Oksenkrug G.F. summarized their experience and data from their colleagues' research and were among the first to provide consistent evidence of the involvement of serotonergic mechanisms in the development of depression [10]. The studies by Professor Lapin I.P. made a significant contribution to the improvement of our understanding of the pathogenesis of depression; in this context, determining their role in the formation of modern concepts of the pathogenesis of depression and the development of psychopharmacology is of particular interest.

This study aims to analyze the contribution of Lapin I.P. and his research team to the development of experimental approaches for studying the mechanisms of depression.

METHODS

Articles and monographs written by the professor personally or in co-authorship, available in PubMed, Google Scholar, eLIBRARY.RU databases, as well as in the bibliographic collection of the V.M. Bekhterev National Medical Research Centre for Psychiatry and Neurology, were analyzed. The studies included in the review were systematized by the authors on the basis of the three main aspects of the professor's scientific research into the pathogenesis of depression: location of abnormalities; improvement of experimental methods; and systematic analysis of the information known in the 1960s about the pathogenesis of depression. The landmark publication by Lapin I.P. and Oksenkrug G.F. "Intensification of the central serotoninergic processes as a possible determinant of the thymoleptic effect" [10], which appeared as a result of scientific work within the framework of the latter direction, was analyzed for semantic groups of scientific papers citing it according to the Semantic Scholar scientometric database in 2022.

RESULTS

Research into the role of brain structures in the pathogenesis of depression in animal models

Professor Lapin I.P. in collaboration with Allikmets L.H. (an Honored Scientist of the Estonian SSR, physician-researcher in the field of the clinical pharmacology of antidepressants and neuroleptics), tested the hypothesis of the possible involvement of the hypothalamus and the amygdala complex in the etiology of depression and the effects of antidepressants. While studying the behavior of amygdala-lesioned rats and their responses to thymoleptics, the authors concluded that these compounds exert their action outside the amygdala [13], in particular by affecting self-stimulation of the lateral hypothalamic regions. When analyzing the results of the chemical stimulation of limbic structures and the hypothalamus in cats [14], the research team hypothesized that the final common pathway of depression, regardless of its etiology, involves decreased activity of the hypothalamus and the dorsomedial amygdala, and increased activity of the basolateral amygdala.

During experiments with the chemical stimulation of the hypothalamus, septum, and amygdala [15] of cats using a serotonin solution combined with intramuscular administration of imipramine, a sharp intensification of autonomic symptoms was noted, which opened the way to suggest the existence of synergism between the action of tricyclic antidepressants and serotonin [16]. A study of rat behavioral patterns following the destruction of specific regions of limbic structures [17] led to the conclusion that the hippocampus is involved in the regulation of emotional behavior.

Use of animal models in studies of the pathogenesis of depression

In the early 1980s, the Professor Lapin I.P. and his colleagues investigated the role of serotonin in the pathogenesis of depression, an effort that led to the development of a model in which experimental animals were subjected to a diet devoid of tryptophan, the amino acid precursor of serotonin [10, 18]. The model of tryptophan depletion has become a widely used animal model of depression [19–21], as it reliably induces a transient drop in serotonin levels and depression-like behavior seen in humans, such as reduced activity and increased immobility.

Formulation of the serotoninergic theory of the pathogenesis of depression

The enhancement of serotonin's autonomic effects and the potentiation of reserpine's sedative action observed in imipramine studies prompted Lapin I.P. and Oksenkrug G.F. to further investigate the role of serotonin in the development of depression. This led to the important publication of their joint paper, "Intensification of the central serotoninergic processes as a possible determinant of the thymoleptic effect", in The Lancet journal [10]. Over the years since the publication of the article, it has been cited numerous times and, thus, has influenced research in the fields of neuropharmacology and psychiatry. Research based on the serotonergic hypothesis outlined in the article has covered a wide range of issues from studying molecular mechanisms to clinical research aimed at optimizing the treatment of depression.

Based only on the data from Semantic Scholar, we were able to identify about 500 studies that had cited this article by 2022 (Appendix S1 in the Supplementary). Those publications can be divided into several groups:

1. Studies related to the etiology and pathogenesis of psychiatric disorders. This group included works on the pathogenesis of affective disorders and neurotransmitter metabolism, as well as studies on animal models of the serotonin model of depression — also applied to human research — and critical articles (Figure 1).

2. Clinical publications on psychiatry, neurology, and addiction medicine. Figure 2 illustrates the popularity of the article by Lapin I.P. and Oksenkrug G.F. within this field of research publications.

3. Studies of the pharmacodynamics and therapeutic effects of medicinal products, as well as those describing the action and efficacy of newly developed drugs, primarily in relation to affective disorders. Figure 3 shows the activity of respective citations.

4. General medical issues. This group included theoretical studies from anesthesiology, medical genetics, cardiology, gynecology, allergology, endocrinology, oncology, and gastroenterology. The publications explored and described models of the pathogenesis of mental (predominantly affective) disorders and the evolution of these concepts, fundamental or deontological topics, as well as materials where the subject of research extended beyond neuroscience but, nevertheless, touched upon the serotonergic hypothesis (Figure 4).

DISCUSSION

Based on the results of this review, it appears legitimate to conclude that the work of Lapin I.P. and his team was key in deepening our scientific understanding of serotonin's role in the mechanism of depression and in the development of experimental animal models. The contribution of the scientist and his colleagues has become a landmark in the path toward further research into the neurobiological mechanisms underlying depression and the development of new methods for its treatment, as evidenced by the persisting demand for their publication in the international scientific literature for over more than five decades.

The hypothesis proposed by Professor Lapin as regards the importance of reducing hypothalamic activity is echoed in modern concepts of the involvement of the hypothalamic-pituitary-adrenal axis and glucocorticoid receptors in the formation of not only physiological, but also behavioral responses [22]. This significantly outpaced the widespread dissemination of the results obtained in modern neuroimaging studies. Recent studies [23] have validated Professor Lapin's experimental findings

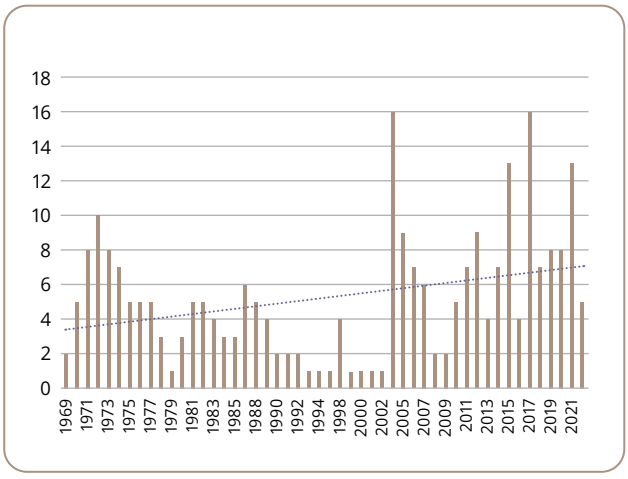

Figure 1. Citations of the paper by Lapin I.P. and Oksenkrug G.F. (1969) over time in articles related to etiology and pathogenesis of psychiatric disorders.

Source: Neznanov et al., 2025.

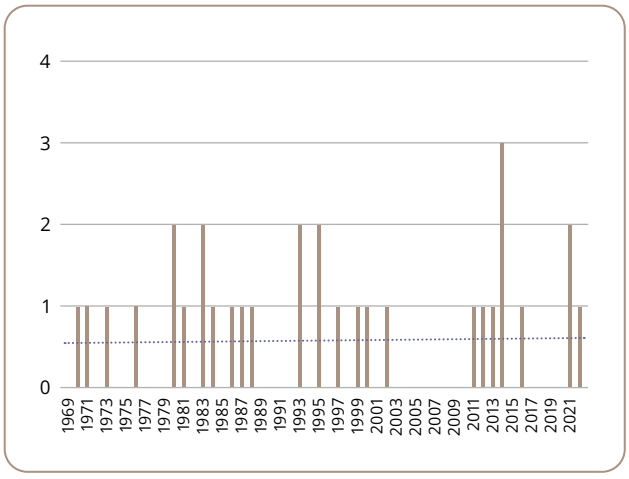

Figure 2. Citations of the paper by Lapin I.P. and Oksenkrug G.F. (1969) over time in articles related to clinical neuroscience.

Source: Neznanov et al., 2025.

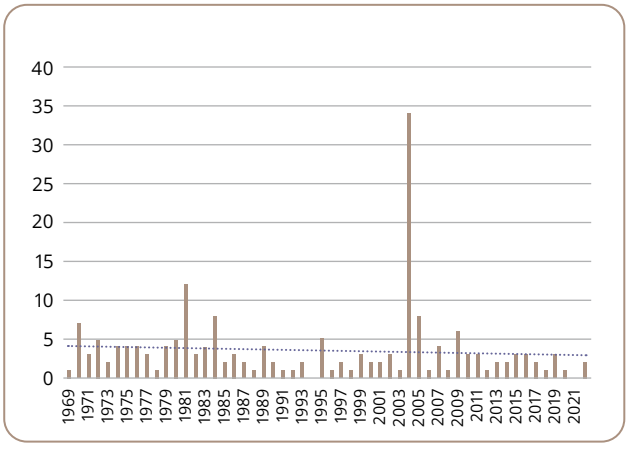

Figure 3. Citations of the paper by Lapin I.P. and Oksenkrug G.F. (1969) over time in articles related to psychopharmacology.

Source: Neznanov et al., 2025.

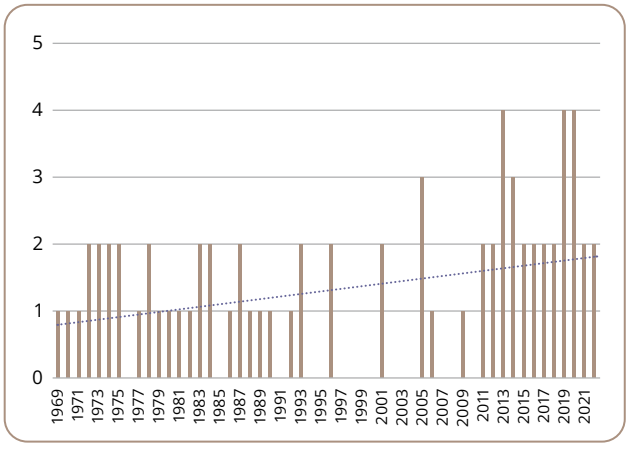

Figure 4. Citations of the paper by Lapin I.P. and Oksenkrug G.F. (1969) over time in broad-subject publications beyond neuroscience.

Source: Neznanov et al., 2025.

regarding the decrease in activity in the dorsomedial part of the amygdaloid complex, which supports mood, alongside an increase in the activity of the basolateral part, which regulates anxiety, stress, and tension. This can explain the existence of several depression subtypes. Specifically, a large neuroimaging project by the ENIGMA Consortium [24] demonstrated a significant decrease in the hippocampal volume in patients with depression compared to the control group. This result aligns with the findings of Lapin I.P. and Allikmets L.H. [17], who showed that the destruction of specific limbic brain structures affects rat behavior, specifically emphasizing the pivotal role the hippocampus plays in the regulation of emotional behavior. The results of the professor's studies also found confirmation in the brain-derived neurotrophic factor (BDNF) theory of depression, which identifies the BDNF as the molecule mostly responsible for the abnormalities that lead to depressive symptoms. What is more, several researchers have suggested that the BDNF plays an important role in the induction of depression in mice: a decrease in hippocampal volume caused by chronic mild stress leads to reduced synaptic transmission and lower BDNF concentration [25].

Since the discovery of antidepressants in the 1950s, their mechanism of action has been the subject of study. One of the main issues for the investigators was a lack

of the corresponding tests and models in experimental pharmacology required for the assessment of the effects of thymoleptics in laboratory animals. This limitation made it difficult to grasp the pharmacodynamics of the drugs and to further work on them. Professor Lapin and colleagues played a significant role in the creation and refinement of animal models of depression during the 1970s and 1980s. Their work was used to investigate the neurobiological mechanisms underlying the disorder and to assess the efficacy of antidepressants. The experimental studies conducted by his team were focused on the use of pharmacological agents such as reserpine [26, 27] to induce depression-like conditions in animals. These were characterized by behavioral changes manifesting as reduced locomotor activity and increased immobility in the forced swimming test. These studies not only helped establish the validity and reliability of animal models of depression, but they also paved the way for the development of new ones: learned helplessness and chronic mild stress, which are widely used in research today [28]. The professor also became known for his contribution to the development of the tryptophan depletion model. Despite technological advances, animal models of depression remain an important tool for studying the pathophysiology of the disorder [29–31], as well as for conducting clinical trials.

According to current scholarship, depression is a complex disorder associated with changes in neurotransmitter systems, signaling pathways in the central nervous system, hormonal dysregulation, epigenetic factors, systemic inflammatory responses, and reduced neuroplasticity [32–34]. The neurogenic theory of depression [35, 36] describes a decrease in the formation of new neurons in the hippocampus. One of the potential pathways that could lead to reduced neurogenesis in the hippocampus and affect catecholamine levels involves the impact on the hypothalamic-pituitary-adrenal axis [35]. Lapin's research into the role of this axis and its connection to reduced catecholamine levels in the brain was an important contribution to our understanding of the mechanism of depression [37].

The analysis and summary of earlier studies, supported by a diverse range of his own research, allowed the professor and his colleagues to lay the foundation for the development of the serotonin theory of depression, which has become a cornerstone in the practical implementation of the most frequently used class of antidepressants today, SSRIs [38].

CONCLUSION

The clinical presentation, etiology, and pathogenesis of depressive disorders have remained the subject of scientific research throughout the history of psychiatry. The steps taken by Lapin I.P. and his team in the 1960s–1980s in their study of the mechanisms of depression development, as well as the research hypotheses they put forth shaped the path of modern research and represent a significant contribution of the Soviet psychopharmacologist to the development of neuroscience. Lapin's work was recognized with numerous awards, including the prestigious Order of Lenin in 1985. The professor's scientific legacy remains of significant importance in the development of scientific practice, even after his death in 2010.

Article history
Submitted: 08 Dec. 2024
Accepted: 29 May 2025
Published Online: 27 Jun. 2025

Authors' contribution: All the authors made a significant contribution to the article, checked and approved its final version prior to publication.

Funding: The materials were prepared with the support of the Federation of European Neuroscience Societies (FENS). "The anniversary of the experiment and the series of scientific publications on the role of serotonin in the development of depression, organized by Iziaslav Lapin" is one of the online projects of 2021 (the creation of a virtual public platform for hosting autobiographies, videos, photographs, and other electronic materials related to renowned neurobiologists and their work), dedicated to the history of neuroscience.

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data
Supplementary material to this article can be found in the online version:
Appendix S1: 10.17816/CP15601-145609

For citation:
Neznanov NG, Tumova MA, Freize VV, Gerasimchuk ES, Radionov DS, Khobeysh MA, Malyshko LV, Anokhina MV, Palchikova EI, Sorokin MYu. Modern Concept of Depression

Pathogenesis: The Contribution of I.P. Lapin's Research Team. *Consortium PSYCHIATRICUM.* 2025;6(2):CP15601. doi: 10.17816/CP15601

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