ISSN 0006-2979, Biochemistry (Moscow), 2024, Vol. 89, No. 11, pp. 1863-1867 © The Author(s) 2024. This article is an open access publication.

MINI-REVIEW

An Intricated *pas de deux* of Addicted Brain and Body Is Orchestrated by Stress and Neuroplasticity

Natalia V. Gulyaeva[1,2,a]* and Danil I. Peregud[1,3]

[1]*Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, 117485 Moscow, Russia*

[2]*Research and Clinical Center for Neuropsychiatry of Moscow Healthcare Department, 115419 Moscow, Russia*

[3]*Federal State Budgetary Institution "V. Serbsky National Medical Research Center for Psychiatry and Drug Addiction" of the Ministry of Health of the Russian Federation, 119034 Moscow, Russia*

[a]*e-mail: nata_gul@ihna.ru*

Received August 13, 2024
Revised August 13, 2024
Accepted August 13, 2024

Abstract—Dependence on psychoactive substances is a phenomenon that is based on the alterations of common molecular and cellular mechanisms, structures and neuronal networks underlying normal brain functioning and realizing stress response, reinforcement and aversion, learning and memory. As a result, aberrant neuroplasticity states associated with somatic changes are formed, which determine the pathogenesis and symptoms of dependence and at the same time can be considered as targets for the development of therapies for such addictions. An integrative scheme of stress and neuroplastic changes participation in the formation of the vicious circle of substance use disorders based on a holistic approach is presented. This special issue of the journal focuses on the molecular mechanisms of psychoactive substance use disorders.

DOI: 10.1134/S0006297924110014

Keywords: psychoactive substances, addiction, substance use disorders, brain, stress, neuroplasticity, neuroendocrine mechanisms

Alcohol kills the nervous cells. All that's left are the calm ones.
(A phrase attributed to Bernard Shaw)

INTRODUCTION

This issue of Biochemistry (Moscow) focuses on the molecular mechanisms of substance use disorders (SUDs). Psychoactive substances (PASs) are chemical compounds with different pharmacodynamic properties and molecular targets, united by the ability to induce a sense of satisfaction and euphoria, which in chronic use may be accompanied by the development of pathological dependence [1]. The formation of dependence on PASs (alcohol, drugs, non-narcotic PASs) is a chronic relapsing process in biologically predisposed individuals, in which PASs in the presence of specific external stimuli cause generally similar adaptation processes at the molecular, cellular, and functional levels.

SUBSTANCE USE DISORDERS AS A PART OF PLASTICITY–PATHOLOGY CONTINUUM: A CHOLISTIC APPROACH

Adaptation processes in the brain are realized in the form of neuroplasticity, which encompasses a variety of processes at the levels from molecules to neural networks [2]. From the point of view of integrative neurobiology, the concept of the continuum of neuroplasticity and neuropathology was created. It is obvious that the commonality and pleiotropy

Abbreviations: HIP, hippocampus; HPA axis, hypothalamic-pituitary-adrenal axis; PAS, psychoactive substance; PFC, prefrontal cortex; SUD, substance use disorder.

* To whom correspondence should be addressed.

of mechanisms at the molecular, synaptic, cellular, and network levels are associated with high adaptive plasticity of a number of cerebral regions (e.g., the hippocampus, HIP) responsible for brain integrative function, including learning and memory [3]. Importantly, the price of high plasticity is the selective sensitivity of these structures to the development of various pathological processes.

Difficulties in the treatment and prevention of dependence on PASs are related to the complexity and multidimensionality of the mechanisms underlying development of such dependencies, as well as multiple states in the continuum of plasticity–pathology, which develop on the basis of fundamental physiological mechanisms of brain functioning, such as stress-responsiveness, reinforcement and aversion, learning and memory. The holistic approach (the term "holism" was introduced in 1926 by J. Smuts) [4], which integrates various mechanisms and aspects of dependence development, seems to be an adequate analytical tool that allows taking into account the multifactorial and multistage nature of the addiction phenomenon and to understand how brain functioning changes sequentially from alterations in genome activity, biochemical changes, remodeling of neuronal connections to transition of behavioral acts to a new level [5].

This approach is all the more important because the formation of SUDs occurs as a result of close interaction between central and peripheral systems. The review [6] in this issue presents the current understanding of the molecular mechanisms that underlie the interaction between visceral systems and central mechanisms of chemical dependence. SUDs are associated with altered plasticity of specific brain structures, with the development of dependence accompanied by stress responses, adaptive processes, learning and memory processes. The realization of all these changes and events is controlled by the central neurohumoral stress-realizing system, the hypothalamic-pituitary-adrenal (HPA) axis. This system is closely associated with immune responses, inflammatory processes and functions as a key regulator of the most important events triggering plastic changes in the brain – systemic inflammatory processes and neuroinflammation [7]. This issue presents a review [8], as well as studies concerning the role of inflammatory processes in the pathogenesis of alcohol dependence in clinic [9] and animal model experiments [10, 11].

VICIOUS CIRCLE OF SUBSTANCE USE DISORDERS

Figure 1 presents an integrative scheme of the involvement of stress and neuroplastic changes in the formation of the vicious circle of the SUDs resulting from changes in the plasticity of the main brain structures implicated. Either directly or indirectly, PASs stimulate dopaminergic projections of the ventral tegmental area (VTA) to the striatum (STR) and prefrontal cortex (PFC), which is the key mechanism of reinforcement [12, 13]. PASs affect the reward system, which is normally targeted by natural stimuli [14], but the degree of PAS effects is significantly higher [15]. With a combination of external (stress [16]) and internal (genetic predisposition [17]) factors, voluntary chronic intoxication becomes possible, which over time can become uncontrollable and is accompanied by the development of tolerance and the formation of stable conditional associative connections [18]. It is believed that at this stage the stress-reactive HPA axis, the PFC as a decision-making center, and the HIP as a key structure for learning and memory are involved.

Changes in expressed gene pattern in specific parts of the brain, epigenetic alterations, disturbances in the neurochemical systems of biogenic amines, neuropeptides, excitatory and inhibitory amino acids (in this issue, these aspects are the subject of [19-21]), disturbances in trophic regulation of neurons, development of the inflammatory process, and as a result, active structural and functional reorganizations of the mesocorticolimbic system are the basis of the adaptation processes in the central nervous system underlying its conversion to functioning under chronic PAS intoxication [22, 23]. Disorders developing as a result of PAS abuse are considered as a pathological form of learning and memory consolidation, accompanied by changes in the synaptic contact architecture as a result of adaptive processes in the intracellular signaling cascades of dopaminergic neurons, primarily in the cascade of protein kinase A – transcription factor CREB [24].

The cessation of PAS intake in a dependent person is accompanied by a deficit of positive reinforcement and the development of a painful withdrawal syndrome, which has both physiological manifestations and an evident affective component. Withdrawal state is an additional stressogenic factor and the basis for the formation of negative reinforcement. The key role in the development of the affective component of withdrawal is attributed to the amygdala (amygdalar complex) and HPA axis [25]. Based on the concept of addiction as an aberrant form of learning and memory, the combination of conditional and unconditional stimuli leads to memory reconsolidation, which is a trigger for relapse. The amygdala, HIP, and STR are key structures of this process, and signal cascades initiated by dopamine and glutamate receptors are its molecular basis [26]. Relapse has also been associated with a declining of PFC control [27]. Increase of stressor influence, development of depressive symptoms, which are accompanied by activation of HPA axis, decrease of trophic regulation and atrophy of frontal cortical areas are predictors of relapse [28]. The series

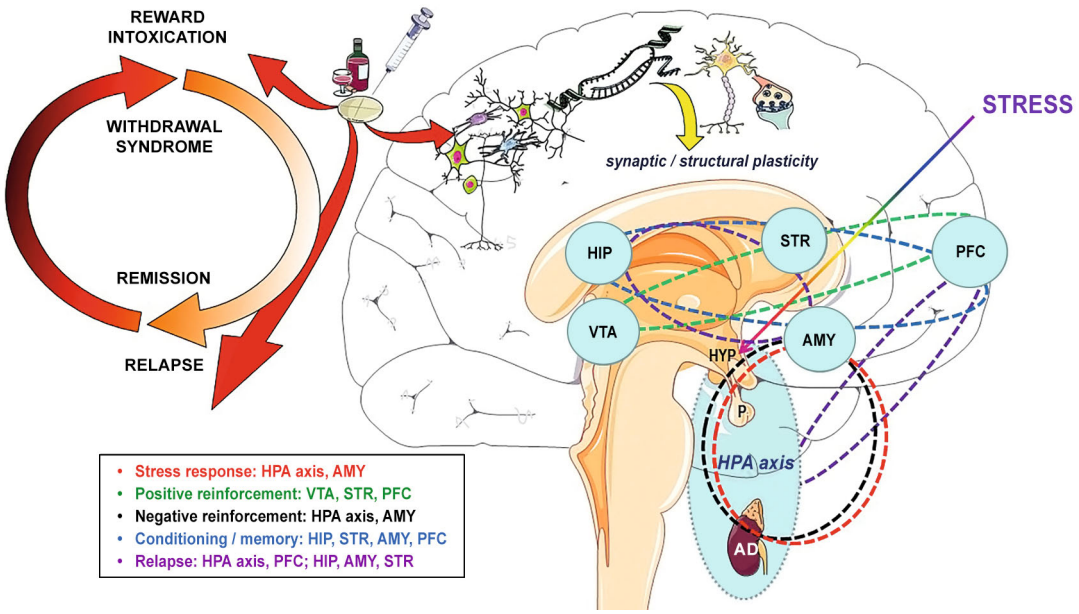

Fig. 1. Involvement of stress and neuroplastic changes in the formation of the substance use disorders (SUD) vicious circle: a holistic approach. The development of SUDs is based on fundamental mechanisms of normal brain functioning, including stress response, reinforcement (positive and negative), learning, and memory. Various PAS, along with specific effects, induce typical adaptive and pathological changes in neuroplasticity at the molecular, epigenetic, cellular and functional levels. During the development of dependence on PAS, the key mechanism of their influence on positive reinforcement system is the stimulation of dopaminergic projections of the ventral tegmental area (VTA) into the striatum (STR) and the effect on the prefrontal cortex (PFC). Stressors [their action is mediated by the stress-reactive hypothalamic-pituitary-adrenal axis (HPA axis; HYP, hypothalamus; P, pituitary; AD, adrenals)] interacting with the amygdala (AMY) nuclei contribute to voluntary chronic PAS intoxication becoming uncontrollable. This is accompanied by the development of tolerance to PAS and formation of conditioned associative connections by comprising the system of key structures for learning and memory (hippocampus, HIP, PFC, and AMY) closely interacting with HPA axis. When dependence on PAS is formed, stopping PAS intake is accompanied by the development of withdrawal syndrome manifested at both physiological and affective levels and associated with a decrease in positive reinforcement. Withdrawal becomes a new severe stressor and the basis for negative reinforcement mediated by HPA axis and AM. HPA axis dysfunction is also associated with the manifestation of relapse related with weakened PFC control. A physiologic trigger of relapse is memory reconsolidation, and key structures are AM, HIP, and STR. Neuroplasticity changes associated with the development of addiction span all levels, from epigenetic, molecular, and synaptic to cellular and network. Chronic PAS intoxication induces both adaptive and pathological changes in the expression of various genes, alterations in neurotransmitter and trophic factor systems, development of inflammatory process and, as a result, structural and functional rearrangements of involved structures. Attributable to a healthy brain functional pleiotropy of brain structures involved in stress, adaptation, learning, and memory, plays a vital role in the formation of SUDs, on the one hand ensuring the adaptation to PAS intoxication, and on the other hand forming pathological phenotype of addiction. As a result, dependence on PASs is realized on the basis of fundamental mechanisms of normal brain functioning by inducing aberrant plasticity. The integrative scheme presented is based on the data from [12, 13, 18, 25-28] and uses templates of Servier Medical Art (Servier), provided by Creative Commons Attribution 3.0 unported license.

of positive and negative reinforcement shapes associative links of dependence and disrupts homeostatic mechanisms of central nervous system functioning [29]. Thus, SUD represents a vicious circle consisting of cycles of intoxication and abstinence involving anatomical substrates specific to each act (Fig. 1).

As the duration of abstinence increases, structural and functional abnormalities in the central nervous system gradually recover [30]. In other words, if we exclude PAS intake in the absence of significant organic damage, the brain will reach, if not the initial parameters of functioning, then at least maximally approach them. The key aspect of addiction is the craving to the substance, which, given a combination of external circumstances and internal readiness, will lead to the realization of the motivational act and subsequent relapse. One of the main goals of therapy is to stabilize remission, prevent memory reconsolidation, and reduce craving and motivation to use. The development of approaches to pathogenetically justified therapy for SUDs is based, among other things, on understanding the important role of neurotrophic factor system alterations in the development of dependence on PAS [31]. In this issue, we present a paper showing that low-molecular-weight mimetics of neurotrophin-3 attenuate somatic manifestations of morphine withdrawal syndrome in rats [32]. On the other hand, an important problem is the search for new biomarkers reflecting the processes occurring in the brain during the formation of dependence on PAS. In this issue,

a review article on small extracellular vesicles in peripheral blood is devoted to this aspect [33].

CONCLUSIONS: MULTIPLE DIMENSIONS OF SUBSTANCE USE DISORDERS

To summarize, we can conclude that SUDs are a truly amazing phenomenon, which is based on the usurpation by PAS of common molecular and cellular mechanisms, structures, and neuronal networks fundamental to the normal functioning of the brain and representing the basis for stress response, reinforcement and aversion, learning, and memory. As a result, aberrant plasticity states associated with somatic changes are formed, which underlie the pathogenesis and symptomatology of dependence on PAS and, at the same time, are targets for the development of therapies. Importantly, common mechanisms of pathogenesis at the molecular, cellular and network levels explain the high frequency of comorbidity between dependence on PASs and many other psychiatric disorders [17, 34, 35].

Contributions. N.V.G. concept, search and analysis of data, final editing of the article; D.I.P. concept, search and analysis of data, writing the primary text.

Funding. This study was supported by the Moscow Center for Innovative Technologies in Healthcare (research project no. 0702-1/23).

Ethics declarations. This work does not contain any studies involving human and animal subjects. The authors of this work declare that they have no conflicts of interest.

REFERENCES

1. Ciucă Anghel, D. M., Nițescu, G. V., Tiron, A. T., Guțu, C. M., and Baconi, D. L. (2023) Understanding the mechanisms of action and effects of drugs of abuse, *Molecules*, **28**, 4969, https://doi.org/10.3390/molecules28134969.
2. Gulyaeva, N. V. (2017) Molecular mechanisms of neuroplasticity: An expanding universe, *Biochemistry (Moscow)*, **82**, 237-242, https://doi.org/10.1134/S0006297917030014.
3. Gulyaeva, N. V. (2022) Multi-level plasticity-pathology continuum of the nervous system: functional aspects, *Neurochem. J.*, **16**, 424-428, https://doi.org/10.1134/S1819712422040092.
4. Smuts, J. C. (1926) *Holism and Evolution*, Macmillan and Co., Limited, London.
5. Valentino, R. J., Nair, S. G., and Volkow, N. D. (2024) Neuroscience in addiction research, *J. Neural. Transm. (Vienna)*, **131**, 453-459, https://doi.org/10.1007/s00702-023-02713-7.
6. Peregud, D. I., and Gulyaeva, N. V. (2024) Contribution of visceral systems to the development of substance use disorders: translational aspects of interaction between central and peripheral mechanisms, *Biochemistry (Moscow)*, **89**, 1868-1888, https://doi.org/10.1134/S0006297924110026.
7. Gulyaeva, N. V. (2023) Glucocorticoids orchestrate adult hippocampal plasticity: growth points and translational aspects, *Biochemistry (Moscow)*, **88**, 565-589, https://doi.org/10.1134/S0006297923050012.
8. Mikhalitskaya, E. V., Vyalova, N. M., Bokhan, N. A., and Ivanova, S. A. (2024) Alcohol-induced activation of chemokine system and neuroinflammation development, *Biochemistry (Moscow)*, **89**, 1889-1903, https://doi.org/10.1134/S0006297924110038.
9. Prokopieva, V. D., Vetlugina, T. P., Epimakhova, E. V., Boiko, A. S., and Bokhan, N. A. (2024) Association of peripheral markers of oxidative stress with clinical parameters and inflammatory factors in alcoholic patients, *Biochemistry (Moscow)*, **89**, 1904-1910, https://doi.org/10.1134/S000629792411004X.
10. Airapetov, M. I., Eresko, S. O., Shamaeva, S. A., Bychkov, E. R., Lebedev, A. A., and Shabanov, P. D. (2024) Study of neuroinflammation in the rat hippocampus during ethanol exposure and pharmacological correction with azithromycin: new data and future perspectives, *Biochemistry (Moscow)*, **89**, 1911-1921, https://doi.org/10.1134/S0006297924110051.
11. Shamakina, I. Yu., Anokhin, P. K., Ageldinov, R. A., and Kokhan, V. S. (2024) Neuroimmune characteristics of animals with prenatal alcohol intoxication, *Biochemistry (Moscow)*, **89**, 1922-1929, https://doi.org/10.1134/S0006297924110063.
12. Cooper, S., Robison, A. J., and Mazei-Robison, M. S. (2017) Reward circuitry in addiction, *Neurotherapeutics*, **14**, 687-697, https://doi.org/10.1007/s13311-017-0525-z.
13. Hayes, A., Herlinger, K., Paterson, L., and Lingford-Hughes, A. (2020) The neurobiology of substance use

and addiction: evidence from neuroimaging and relevance to treatment, *BJPsych. Adv.*, **26**, 367-378, https://doi.org/10.1192/bja.2020.68.
14. Tan, B., Browne, C. J., Nöbauer, T., Vaziri, A., Friedman, J. M., and Nestler, E. J. (2024) Drugs of abuse hijack a mesolimbic pathway that processes homeostatic need, *Science*, **384**, eadk6742, https://doi.org/10.1126/science.adk6742.
15. Wightman, R. M., and Robinson, D. L. (2002) Transient changes in mesolimbic dopamine and their association with 'reward', *J. Neurochem.*, **82**, 721-735, https://doi.org/10.1046/j.1471-4159.2002.01005.x.
16. Ruisoto, P., and Contador, I. (2019) The role of stress in drug addiction. An integrative review, *Physiol. Behav.*, **202**, 62-68, https://doi.org/10.1016/j.physbeh.2019.01.022.
17. Miller, A. P., Bogdan, R., Agrawal, A., and Hatoum, A. S. (2024) Generalized genetic liability to substance use disorders, *J. Clin. Invest.*, **134**, e172881, https://doi.org/10.1172/JCI172881.
18. Koob, G. F., and Volkow, N. D. (2010) Neurocircuitry of addiction, *Neuropsychopharmacology*, **35**, 217-238, https://doi.org/10.1038/npp.2009.110.
19. Peregud, D. I., Shirobokova, N. I., Kvichansky, A. A., Stepanichev, M. Yu., and Gulyaeva, N. V. (2024) Purmorphamine alters anxiety-like behavior and expression of hedgehog cascade components in rat brain after alcohol withdrawal, *Biochemistry (Moscow)*, **89**, 1938-1949, https://doi.org/10.1134/S0006297924110087.
20. Vetrovoy, O. V., Potapova, S. S., Stratilov, V. A., and Tyulkova, E. I. (2024) Prenatal hypoxia predisposes to impaired expression of the *chrna4* and *chrna7* genes in adult Rats without affecting acetylcholine metabolism during embryonic development, *Biochemistry (Moscow)*, **89**, 1950-1960, https://doi.org/10.1134/S0006297924110099.
21. Sudakov, S. K., Bogdanova, N. G., Nazarova, G. A., and Zolotov, N. N. (2024) Behavioral features and blood enzyme activity in offspring of rats conceived from an alcohol-intoxicated father, *Biochemistry (Moscow)*, **89**, 1930-1937, https://doi.org/10.1134/S0006297924110075.
22. Korpi, E. R., den Hollander, B., Farooq, U., Vashchinkina, E., Rajkumar, R., Nutt, D. J., Hyytiä, P., and Dawe, G. S. (2015) Mechanisms of action and persistent neuroplasticity by drugs of abuse, *Pharmacol. Rev.*, **67**, 872-1004, https://doi.org/10.1124/pr.115.010967.
23. Nestler, E. J., and Lüscher, C. (2019) The molecular basis of drug addiction: linking epigenetic to synaptic and circuit mechanisms, *Neuron*, **102**, 48-59, https://doi.org/10.1016/j.neuron.2019.01.016.
24. Liu, X., Wang, F., Le, Q., and Ma, L. (2023) Cellular and molecular basis of drug addiction: The role of neuronal ensembles in addiction, *Curr. Opin. Neurobiol.*, **83**, 102813, https://doi.org/10.1016/j.conb.2023.102813.
25. Koob, G. F. (2021) Drug addiction: hyperkatifeia/negative reinforcement as a framework for medications development, *Pharmacol. Rev.*, **73**, 163-201, https://doi.org/10.1124/pharmrev.120.000083.
26. Milton, A. L. (2023) Drug memory reconsolidation: from molecular mechanisms to the clinical context, *Transl. Psychiatry*, **13**, 370, https://doi.org/10.1038/s41398-023-02666-1.
27. Garavan, H., Brennan, K. L., Hester, R., and Whelan, R. (2013) The neurobiology of successful abstinence, *Curr. Opin. Neurobiol.*, **23**, 668-674, https://doi.org/10.1016/j.conb.2013.01.029.
28. Sinha, R. (2011) New findings on biological factors predicting addiction relapse vulnerability, *Curr. Psychiatry Rep.*, **13**, 398-405, https://doi.org/10.1007/s11920-011-0224-0.
29. Ferrer-Pérez, C., Montagud-Romero, S., and Blanco-Gandía, M. C. (2024) Neurobiological theories of addiction: a comprehensive review, *Psychoactives*, **3**, 35-47, https://doi.org/10.3390/psychoactives3010003.
30. Parvaz, M. A., Rabin, R. A., Adams, F., and Goldstein, R. Z. (2022) Structural and functional brain recovery in individuals with substance use disorders during abstinence: a review of longitudinal neuroimaging studies, *Drug Alcohol Depend.*, **232**, 109319, https://doi.org/10.1016/j.drugalcdep.2022.109319.
31. Peregud, D. I., Baronets, V. Y., Terebilina, N. N., and Gulyaeva, N. V. (2023) Role of BDNF in neuroplasticity associated with alcohol dependence, *Biochemistry (Moscow)*, **88**, 404-416, https://doi.org/10.1134/S0006297923030094.
32. Kolik, L. G., Konstantinipolsky, M. A., Nikolaev, S. V., Logvinov, I. O., Antipova, T. A., and Gudasheva, T. A. (2024) Low-molecular neurotrophin-3 mimetics with different patterns of postreceptor signaling activation attenuate differentially morphine withdrawal in rats, *Biochemistry (Moscow)*, **89**, 1961-1969, https://doi.org/10.1134/S0006297924110105.
33. Severtsev, V. V., Pavkina, M. A., Ivanets, N. N., Vinnikova, M. A., and Yakovlev, A. A. (2024) Extracellular vesicles as potential biomarkers in addictive disorders, *Biochemistry (Moscow)*, **89**, 1970-1984, https://doi.org/10.1134/S0006297924110117.
34. Nardi, W. R., Kelly, P., Roy, A., Becker, S., Brewer, J., and Sun, S. (2024) A systematic review and meta-analysis of psychosocial interventions for persons with comorbid anxiety and substance use disorders, *J. Subst. Use Addict. Treat.*, **165**, 209442, https://doi.org/10.1016/j.josat.2024.209442.
35. De Aguiar, A. C. L., and Bloc, L. G. (2024) Transdiagnosis of alcohol use and psychopathologies: a systematic review, *Addict. Behav. Rep.*, **19**, 100543, https://doi.org/10.1016/j.abrep.2024.100543.