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NEUROBIOLOGICAL MECHANISMS OF ALCOHOL ADDICTION FORMATION: THE ROLE OF THE DOPAMINERGIC SYSTEM

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Annotation: Purpose of the study: To investigate the impact of chronic alcohol consumption on the functioning of the dopaminergic system of the brain and to identify key neurobiological markers of addiction formation.

Methods: The study included 156 patients diagnosed with alcohol dependence (mean age 42.3 ± 8.7 years) and 80 individuals in the control group. Functional MRI, plasma dopamine level assessment, and neuropsychological testing were applied.

Results: A statistically significant decrease of 34.2% ($p<0.001$) in the density of D2 receptors in the ventral tegmental area was revealed in patients with alcohol dependence compared to the control group. The basal dopamine level was reduced by 28.6% ($p<0.01$), while a pathological reaction to alcohol-related cues was observed, with an increase of 187% from baseline.

Conclusions: Alcohol dependence is characterized by profound impairments in dopaminergic neurotransmission, which explains the development of compulsive craving and loss of control over alcohol use.

Keywords: alcohol dependence, dopaminergic system, D2 receptors, neurobiology of addiction, functional MRI.

Introduction

Alcohol dependence is a chronic relapsing disorder affecting more than 283 million people worldwide (1). Despite substantial progress in understanding the pathophysiology of addictive disorders, treatment effectiveness remains insufficient, and relapse rates reach 60–80% within the first year after therapy (2, 3).

Modern neurobiological concepts consider alcohol dependence as a result of pathological changes in the brain's reward system (4). The dopaminergic system plays a key role in this process, mediating motivational behavior and the formation of pathological craving (5, 6). Chronic ethanol exposure induces adaptive changes in the mesolimbic dopaminergic system, including the ventral tegmental area (VTA) and nucleus accumbens (7).

Previous studies have demonstrated reduced density of dopamine D2 receptors in individuals with various forms of addiction (8, 9), but specific features of alcohol dependence remain insufficiently studied. Of particular interest is the dynamics of these changes depending on disease severity and duration of abstinence (10).

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Purpose of the study: a comprehensive assessment of the dopaminergic system in patients with alcohol dependence of varying severity using neuroimaging and biochemical methods.

Materials and Methods

Study participants

The study was conducted at the City Narcology Center from January 2022 to December 2023.
Inclusion criteria: age 25–60 years, alcohol dependence diagnosis according to ICD-10 (F10.2), disease duration ≥3 years, abstinence period 14–21 days at the time of examination.
Exclusion criteria: comorbid psychiatric disorders, dependence on other psychoactive substances, severe somatic pathology, contraindications to MRI.

The main group consisted of 156 individuals (121 men, 35 women; mean age 42.3 ± 8.7 years). The control group included 80 healthy volunteers matched by age and sex (59 men, 21 women; mean age 40.8 ± 7.9 years) with no history of alcohol or substance abuse.

Research methods

1. **Functional MRI (fMRI)**

The study was conducted on a 3 Tesla scanner (Siemens Magnetom Skyra).
A protocol with visual alcohol-related stimuli (images of alcoholic beverages and drinking situations) and neutral stimuli was used. Activation of the ventral tegmental area, nucleus accumbens, prefrontal cortex, and amygdala was analyzed (11, 12).

2. PET with [11C]raclopride

To assess the density of D2 receptors, positron emission tomography with the radioligand [11C]raclopride was performed in 68 patients from the main group and 40 individuals from the control group (13).

3. Biochemical studies

Baseline levels of dopamine and its metabolites (homovanillic acid, 3-methoxytyramine) in blood plasma were measured using high-performance liquid chromatography coupled with mass spectrometry (14).

4. Neuropsychological testing

Cognitive functions and impulsivity were assessed using a standardized battery of tests:

- Wisconsin Card Sorting Test,
- Iowa Gambling Task,
- Barratt Impulsiveness Scale (BIS-11),
- Penn Alcohol Craving Scale (15, 16).

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Statistical analysis

Statistical data processing was performed using SPSS 26.0.
Group comparisons were carried out with the Student's t-test for independent samples and the Mann–Whitney U-test.
Correlation analysis was conducted using Pearson's coefficient.
Differences were considered statistically significant at $p < 0.05$.

Results

Neuroimaging data

During fMRI with alcohol-related cues, patients with alcohol dependence demonstrated significantly higher activation of the ventral tegmental area (156% higher compared to controls, $p < 0.001$) and the nucleus accumbens (142% higher, $p < 0.001$).
At the same time, a 38% decrease in activation of the dorsolateral prefrontal cortex was observed ($p < 0.01$), indicating weakened cognitive control (Table 1).

Table 1. Activation of brain structures in response to alcohol-related stimuli

Structure	**Alcohol Dependence Group (BOLD signal, %)**	**Control Group (BOLD signal, %)**	**p-value**
VTA	2.84 ± 0.67	1.11 ± 0.34	<0.001
Nucleus accumbens	3.12 ± 0.89	1.29 ± 0.41	<0.001
DLPFC	1.23 ± 0.45	1.98 ± 0.52	<0.01
Amygdala	2.67 ± 0.71	1.45 ± 0.38	<0.001

PET findings

PET imaging with [11C]raclopride demonstrated a statistically significant reduction in D2-receptor availability in the ventral tegmental area by 34.2% ($p<0.001$) and in the nucleus accumbens by 29.7% ($p<0.001$) in patients with alcohol dependence compared to the control group (Figure 1).
An inverse correlation was found between D2-receptor density and disease duration ($r = –0.58$, $p<0.001$).

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Biochemical parameters

The basal dopamine level in blood plasma was significantly lower in patients with alcohol dependence compared to controls (41.3 ± 12.7 ng/mL vs. 57.8 ± 14.2 ng/mL, $p<0.01$).
Homovanillic acid concentration was also reduced by 23.4% ($p<0.05$).

During experimental exposure to alcohol-related stimuli (visual images and odors), patients in the main group demonstrated a sharp dopamine surge—the level increased to 118.6 ± 28.4 ng/mL (a 187% rise from baseline, $p<0.001$), whereas the control group showed only a minimal response (12% increase, $p>0.05$).

Neuropsychological findings

Patients with alcohol dependence showed markedly higher impulsivity scores on the BIS-11 scale (74.6 ± 11.3 vs. 52.1 ± 9.8 in controls, $p<0.001$).
Reduced cognitive flexibility was observed on the Wisconsin Card Sorting Test (perseverative errors: 28.4 ± 8.9 vs. 15.2 ± 5.6, $p<0.001$) and impaired decision-making on the Iowa Gambling Task (17, 18).

A direct correlation was identified between the degree of D2-receptor reduction and impulsivity severity ($r = 0.64$, $p<0.001$), as well as between the pathological dopaminergic response to alcohol cues and craving intensity measured by the Penn Alcohol Craving Scale ($r = 0.71$, $p<0.001$).

Subgroup analysis by dependence severity

When the main group was divided according to DSM-5 severity criteria (mild, moderate, severe), a progressive pattern of changes was observed.
In patients with severe dependence (n=58), the reduction in D2-receptor density reached 42.6% ($p<0.001$), whereas in those with mild dependence (n=43), it was only 18.3% ($p<0.05$).
These data are presented in Figure 2.

DISCUSSION

The results obtained provide compelling evidence supporting the central role of dopaminergic system dysfunction in the pathogenesis of alcohol dependence and broaden the current understanding of the neurobiological mechanisms underlying addiction formation (19, 20).

Receptor Apparatus Dysfunction

The observed 34.2% reduction in D2 receptor density in key structures of the reward system is consistent with the “reward deficiency syndrome” concept (21). Chronic ethanol-induced stimulation of dopaminergic neurons leads to compensatory downregulation of receptors, resulting in a hypofunctional reward state during abstinence (22, 23).

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This mechanism explains the development of anhedonia, dysphoria, and compulsive alcohol craving as attempts to restore normal dopaminergic neurotransmission. Importantly, the progressive nature of these receptor changes correlates with the severity and duration of the disorder ($r = –0.58$, $p < 0.001$), reflecting neuroplastic processes that stabilize the pathological state and contribute to treatment resistance at later stages (24).

Pathological Stimulus Reactivity

The paradoxical combination of reduced basal dopamine levels and its marked increase (by 187%) in response to alcohol-related cues reflects the phenomenon of sensitization (25, 26). Repeated exposure to alcohol causes a progressive enhancement of dopaminergic responses in the mesolimbic system, forming the basis for pathological craving and loss of control (27).

This mechanism explains “craving” — an intense, often overwhelming desire to consume alcohol triggered by conditioned cues (visual stimuli, drinking environments, social contexts) (28). The strong correlation between dopaminergic reactivity and craving scale scores ($r = 0.71$, $p < 0.001$) underscores its clinical relevance.

Impairment of Cognitive Control

A 38% reduction in dorsolateral prefrontal cortex activation in response to alcohol cues indicates weakened cognitive control and decision-making processes (29, 30). The prefrontal cortex plays a key role in suppressing impulsive reactions and regulating reward-driven behavior (31). An imbalance between the hyperactivated reward system and impaired control mechanisms creates conditions for compulsive alcohol use despite negative consequences (32).

Executive function deficits identified through neuropsychological testing correlate with structural prefrontal cortex alterations observed in chronic alcohol use (33), highlighting the importance of including cognitive training in rehabilitation programs.

Clinical Implications

The findings have significant implications for therapeutic strategy development. Understanding the neurobiological alterations provides justification for pharmacological approaches targeting dopaminergic dysfunction. Drugs modulating D2 receptor activity (such as aripiprazole) may represent promising therapeutic agents for alcohol dependence (34, 35).

Additionally, neuromodulation techniques, including transcranial magnetic stimulation of the dorsolateral prefrontal cortex, have demonstrated efficacy in reducing alcohol craving and may serve as an adjunct component of treatment (36, 37).

Study Limitations

The limitations of this study include the relatively small size of the subgroup undergoing PET imaging ($n = 68$) and the fixed abstinence period (14–21 days) at the time of assessment. Longitudinal evaluation across different stages of dependence and recovery could provide

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additional insights into neuroplasticity. Genetic factors potentially influencing individual variability in dopaminergic function should also be considered (38, 39).

Conclusion

This study demonstrates that alcohol dependence is characterized by profound and progressive disturbances in dopaminergic neurotransmission, including reduced D2 receptor density, pathological cue reactivity, and impaired cognitive control. Together, these alterations form the neurobiological substrate of compulsive craving and loss of control over alcohol use.

The findings support the need for a comprehensive therapeutic approach combining pharmacological correction of neurotransmitter imbalance with non-pharmacological methods aimed at cognitive restoration and neuromodulation. Future research should focus on the dynamics of neurobiological changes during recovery and the development of personalized treatment strategies based on the patient's individual neurobiological profile.

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