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EVALUATION OF ETHANOL ADMINISTRATION IN SWISS MICE AFTER CHRONIC ANTIANXIETY TREATMENT

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ABSTRACT

Alcohol use disorder (AUD) is frequently associated with anxiety disorders, and the interaction between anxiolytic medications and ethanol consumption remains poorly understood. Clonazepam, a benzodiazepine that enhances γ-aminobutyric acid (GABA)-mediated neurotransmission, shares several neuropharmacological mechanisms with ethanol and may influence alcohol-seeking behavior. The present study investigated the effects of chronic clonazepam treatment on ethanol self-administration, ethanol intake, and anxiety-like behavior in Swiss albino mice. Male Swiss mice were trained to self-administer a 10% (w/v) ethanol solution using an operant conditioning paradigm. Following the establishment of stable baseline ethanol consumption, animals received clonazepam (0.5 mg/kg, i.p.) or vehicle according to the experimental protocol. Ethanol rewards, ethanol intake, water consumption, and total fluid intake were monitored throughout the study. Anxiety-like behavior was assessed using the Elevated Plus Maze (EPM), while locomotor activity was evaluated using an actophotometer. Blood ethanol concentrations were measured to validate ethanol self-administration behavior. Chronic clonazepam treatment significantly altered ethanol consumption patterns. Acute clonazepam exposure initially reduced ethanol self-administration and intake; however, prolonged treatment produced a significant increase in ethanol rewards, ethanol intake, and ethanol preference compared with baseline and vehicle-treated controls ($p < 0.05$). A significant positive correlation was observed between ethanol rewards and blood ethanol concentrations ($p < 0.0001$). In the EPM, clonazepam-treated mice spent significantly more time in the open arms and less time in the closed arms, indicating marked anxiolytic-like activity. No significant changes in locomotor activity were observed. These findings demonstrate that chronic clonazepam treatment exerts a biphasic effect on ethanol consumption while maintaining anxiolytic efficacy. Long-term benzodiazepine exposure may enhance alcohol-directed behaviors, highlighting potential implications for the management of anxiety disorders coexisting with alcohol use disorder.

KEYWORDS: Ethanol; Clonazepam; Alcohol self-administration; Anxiety; Elevated Plus Maze; Benzodiazepines; Alcohol use disorder.

1. INTRODUCTION

Alcohol use disorder (AUD) is a chronic relapsing condition characterized by compulsive alcohol consumption, impaired control over drinking behavior, and the emergence of negative emotional states during withdrawal. Ethanol is one of the most widely consumed psychoactive substances worldwide and exerts diverse effects on the central nervous system (CNS), including anxiolysis, sedation, motor impairment, cognitive dysfunction, tolerance, and physical dependence (Becker and Lopez, 2004; Abrahao et al., 2017). Repeated ethanol exposure induces neuroadaptive changes in multiple neurotransmitter systems, particularly γ-aminobutyric acid (GABA), glutamate, dopamine, and serotonin pathways, which contribute to the development of tolerance, dependence, and withdrawal symptoms (Koob and Volkow, 2016). Understanding these neurobiological adaptations is essential for the development of effective therapeutic interventions for alcohol-related disorders.

Anxiety disorders frequently coexist with alcohol misuse, and accumulating evidence suggests a bidirectional relationship between anxiety and alcohol consumption. Acute ethanol administration produces anxiolytic-like effects primarily through facilitation of GABAA receptor-mediated neurotransmission and suppression of excitatory glutamatergic signaling (Gameiro et al., 2003; Campbell et al., 2006). However, prolonged ethanol exposure results in compensatory neurochemical adaptations that diminish its anxiolytic efficacy and promote tolerance. Furthermore, ethanol withdrawal is associated with heightened anxiety, stress responsiveness, and emotional dysregulation, all of which contribute significantly to relapse and the maintenance of alcohol dependence (Becker, 2012). Consequently, understanding the interaction between anxiolytic drugs and ethanol remains an important area of neuropharmacological research.

Benzodiazepines are among the most widely prescribed anxiolytic agents and exert their therapeutic effects through positive allosteric modulation of GABAA receptors. Clonazepam, a long-acting benzodiazepine, is commonly used in the management of anxiety disorders, panic disorders, and seizure-related conditions. Given that both ethanol and benzodiazepines act on GABAergic neurotransmission, chronic administration of anxiolytic agents may influence ethanol consumption, reward-related processes, and anxiety-associated behaviors (Licata and Rowlett, 2008).

Nevertheless, the behavioral consequences of prolonged anxiolytic treatment on ethanol intake and ethanol-induced behavioral responses remain incompletely understood.

Experimental animal models provide valuable tools for investigating the neurobehavioral mechanisms underlying alcohol consumption and anxiety-related behaviors. Voluntary ethanol self-administration paradigms possess considerable face validity for modeling human alcohol-seeking and alcohol-consuming behaviors and have been extensively employed to examine the reinforcing properties of ethanol (Vena and Gonzales, 2015). Likewise, the Elevated Plus Maze (EPM) is a well-established and validated behavioral paradigm for assessing anxiety-like behavior in rodents and has been widely used to evaluate the anxiolytic and anxiogenic effects of pharmacological interventions (Walf and Frye, 2007). The combination of ethanol self-administration and EPM testing provides a comprehensive approach for evaluating the interaction between alcohol consumption and anxiety-related responses.

Therefore, the present study was designed to evaluate ethanol consumption in Swiss mice following chronic anxiolytic treatment with clonazepam. Additionally, the study aimed to investigate the effects of acute and chronic ethanol exposure on anxiety-like behavior using the Elevated Plus Maze and to determine whether chronic anxiolytic treatment

modifies ethanol-induced behavioral responses. Understanding these interactions may provide important insights into the neurobiological mechanisms linking anxiety and alcohol use and may facilitate the development of improved therapeutic strategies for alcohol use disorders.

2. MATERIALS AND METHODS

2.1. Animals

The experiments were conducted in accordance with the guidelines of the Committee for the Control and Supervision of Experiments on Animals (CCSEA), Ministry of Environment, Forest and Climate Change, Government of India, and were approved by the Institutional Animal Ethics Committee (IAEC). Healthy adult male Swiss albino mice weighing 20–25 g were used in the study. Animals were housed in groups of six to seven per polypropylene cage under controlled laboratory conditions (22 ± 2°C; relative humidity 65 ± 5%) with a 12 h light/dark cycle (lights on from 07:00 to 19:00 h). Standard pellet diet and water were provided ad libitum. All animals were drug-naïve and had not been subjected to any prior experimental procedures. Mice were acclimatized to the experimental room for at least 1 h before behavioral testing.

2.2. Drug and Chemicals

Ethanol, clonazepam, and the selected dopaminergic receptor agonists and antagonists were procured from Sigma-Aldrich (USA). All drugs were freshly prepared in 0.9% normal saline before administration. The doses used in the present study were selected based on published literature and preliminary experiments. Drugs were administered either intraperitoneally (i.p.) at a volume of 5 mL/kg body weight or orally, depending on the experimental protocol.

2.3. Elevated Plus Maze (EPM)

Anxiety-like behavior was assessed using the Elevated Plus Maze (EPM), a widely accepted behavioral model for evaluating anxiety in rodents. The apparatus consisted of two open arms (30 × 5 cm) and two closed arms (30 × 5 × 25 cm) connected by a central platform (5 × 5 cm) and elevated 30 cm above the floor. Rodents naturally avoid open and elevated spaces because of their innate fear of predation and exposure. Therefore, anxiety-like behavior was assessed during a 5-min test session by recording the number of entries and time spent in the open and closed arms.

2.4. Statistical analysis

Data are expressed as mean ± standard error of the mean (SEM). Statistical analyses were performed using GraphPad Prism software (GraphPad Software, USA). Differences among groups were analyzed using one-way or two-way analysis of variance (ANOVA), as appropriate, followed by Tukey's multiple comparison test. A value of $p < 0.05$ was considered statistically significant.

3. EXPERIMENTAL PROTOCOL

3.1. Ethanol administration training:

Following an initial week of ethanol exposure, mice underwent daily 30-min operant self-administration sessions for 10 consecutive days, followed by two sessions per week for an additional 15 sessions until stable ethanol responding was achieved. Mice were trained to self-administer a 10% (w/v) ethanol solution and water under a fixed-ratio 1 (FR-1) schedule of reinforcement, in which each operant response resulted in the delivery of 0.1 mL of the respective solution.

Self-administration sessions were conducted in standard operant conditioning chambers housed within sound- and light-attenuating cubicles, as previously described (Roltsch et al., 2014).

3.2. Effects of clonazepam treatment on ethanol administration:

After stable ethanol self-administration was established, animals remained in their home cages for 30 days and were handled twice weekly. Subsequently, mice received daily injections of clonazepam (0.5 mg/kg, i.p.) or vehicle (10 mL/kg, i.p.) and were tested for ethanol self-administration twice weekly. Clonazepam or vehicle was administered 15 min before each 30-min operant session. This interval was selected based on previous studies demonstrating peak brain concentrations of clonazepam approximately 15 min after administration.

Following the baseline period, mice were randomly assigned to one of three groups (n = 6 per group):

1. **Vehicle group:** received vehicle throughout the study period.
2. **Early clonazepam group:** received clonazepam during the initial treatment phase followed by vehicle administration during the later phase.
3. **Late clonazepam group:** received vehicle during the initial phase followed by clonazepam treatment during the later phase.

To confirm that operant responding accurately reflected ethanol intake, blood samples were collected at the end of the final baseline session and the penultimate post-baseline session for determination of blood ethanol concentrations, as described previously (Avegno and Gilpin, 2019).

3.3. The effects of ethanol and clonazepam interaction on anxiety-like behaviors:

The day following the 25th post-baseline operant session, anxiety-like behavior was assessed using the Elevated Plus Maze. The apparatus was constructed from black acrylic and consisted of two open arms and two closed arms elevated 30 cm above the floor. Each mouse was placed individually on the central platform facing an open arm and allowed to freely explore the maze for 5 min.

Behavioral testing was conducted in a sound-attenuated room under low illumination (10–15 lux). The Elevated Plus Maze is a validated behavioral model of anxiety, in which increased time spent in the open arms is interpreted as reduced anxiety-like behavior.

All tests were performed under drug-free conditions at the same time of day as the operant self-administration sessions.

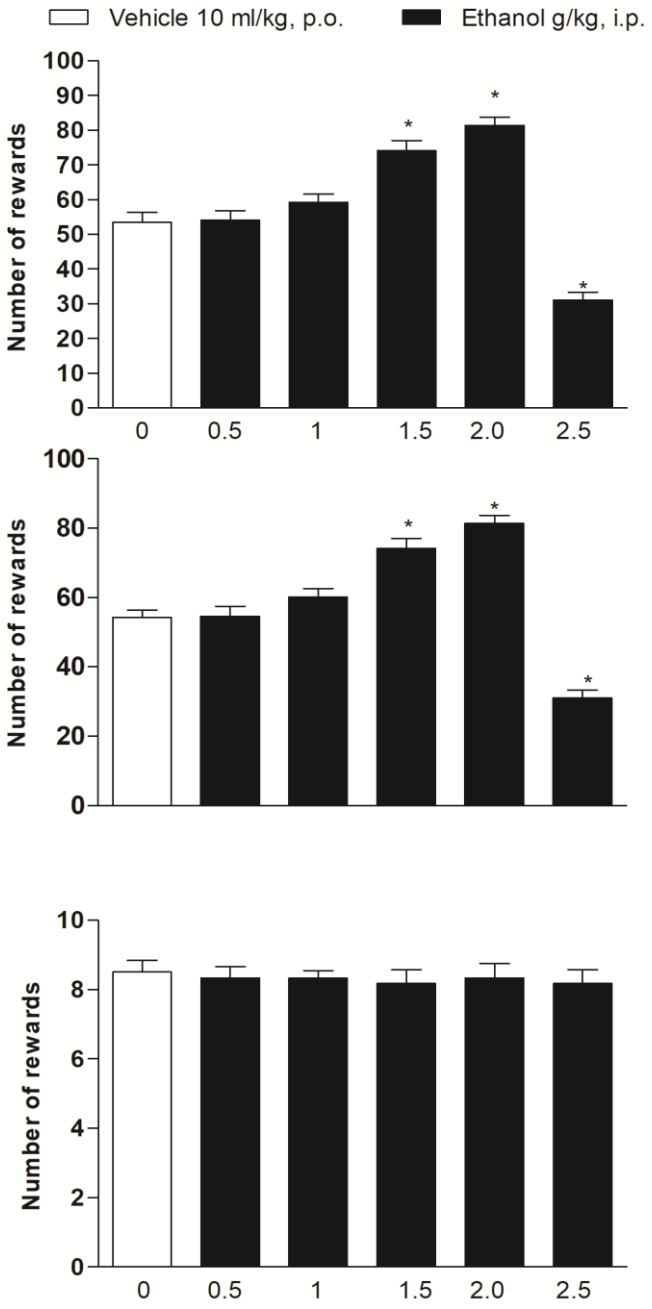
On the day of behavioral testing, animals were not subjected to ethanol self-administration, and clonazepam or vehicle injections were administered 1 h after completion of the EPM test. Control animals were tested under identical conditions.

The time spent in the open and closed arms and the number of arm entries (defined as placement of all four paws into an arm) were recorded by an observer blinded to treatment allocation. Locomotor activity was assessed separately using an actophotometer to exclude nonspecific effects on motor performance.

4. RESULTS

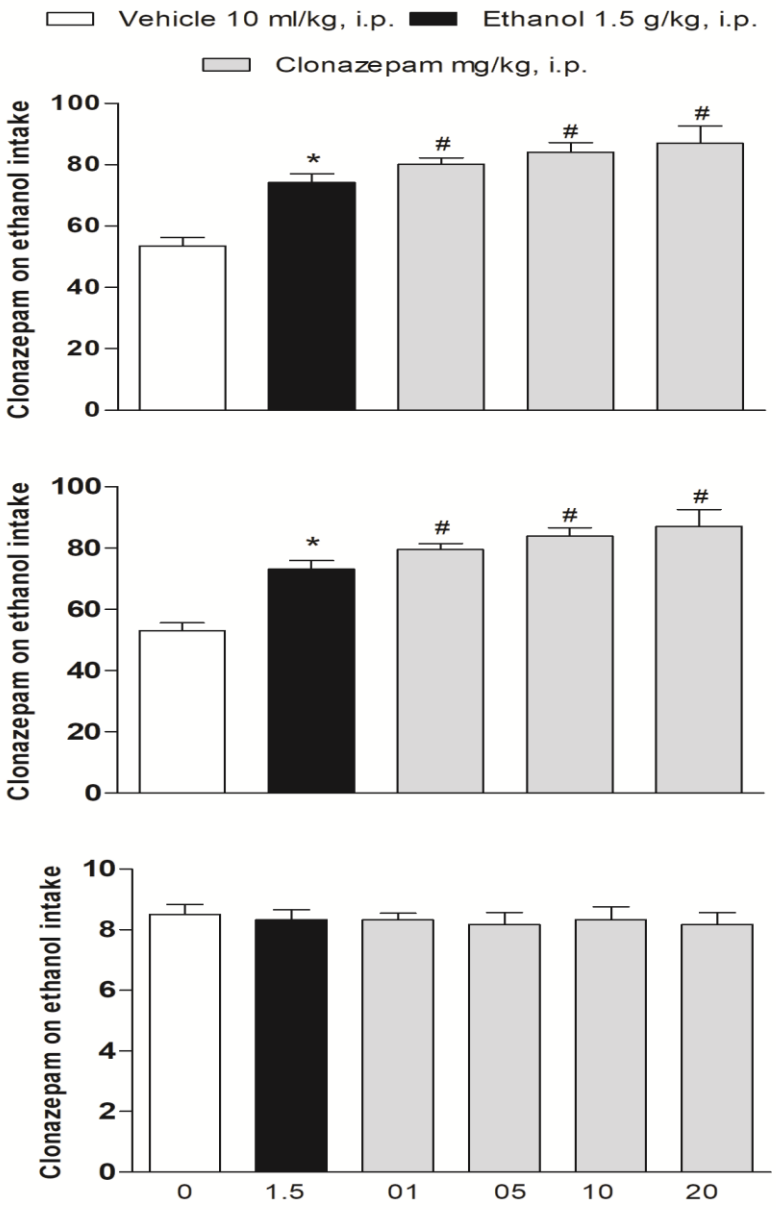
4.1. Effects of clonazepam on ethanol administration

As shown in **Figure 1**, two-way ANOVA revealed significant effects of session ($F(30,540)=6.964$, $p<0.0001$), treatment group ($F(2,18)=5.478$, $p=0.0139$), and session × group interaction ($F(60,540)=10.92$, $p<0.0001$). Acute clonazepam treatment significantly reduced ethanol self-administration during the initial treatment sessions, whereas prolonged administration increased ethanol rewards in both early and late clonazepam-treated groups. Linear regression analysis demonstrated a significant positive correlation between ethanol rewards and blood ethanol concentrations during both baseline and post-baseline sessions ($p<0.0001$).



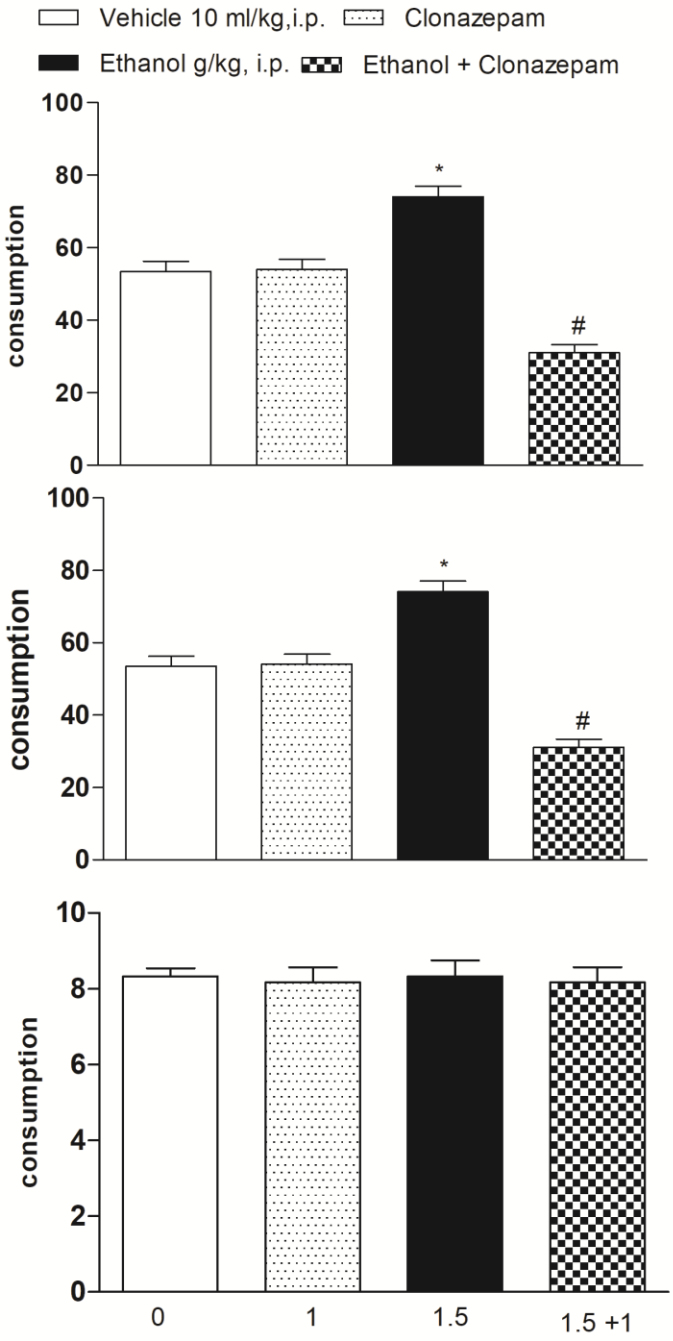
4.2. Effects of Clonazepam on Ethanol Intake

As illustrated in **Figure 2**, ethanol intake (g/kg) was significantly affected by session ($F(30,540)=6.824$, $p<0.0001$), treatment group ($F(2,18)=8.664$, $p=0.0023$), and session × group interaction ($F(60,540)=12.47$, $p<0.0001$). Clonazepam initially reduced ethanol intake, followed by a significant increase during prolonged treatment. Vehicle-treated animals exhibited a gradual reduction in ethanol intake throughout the study period.



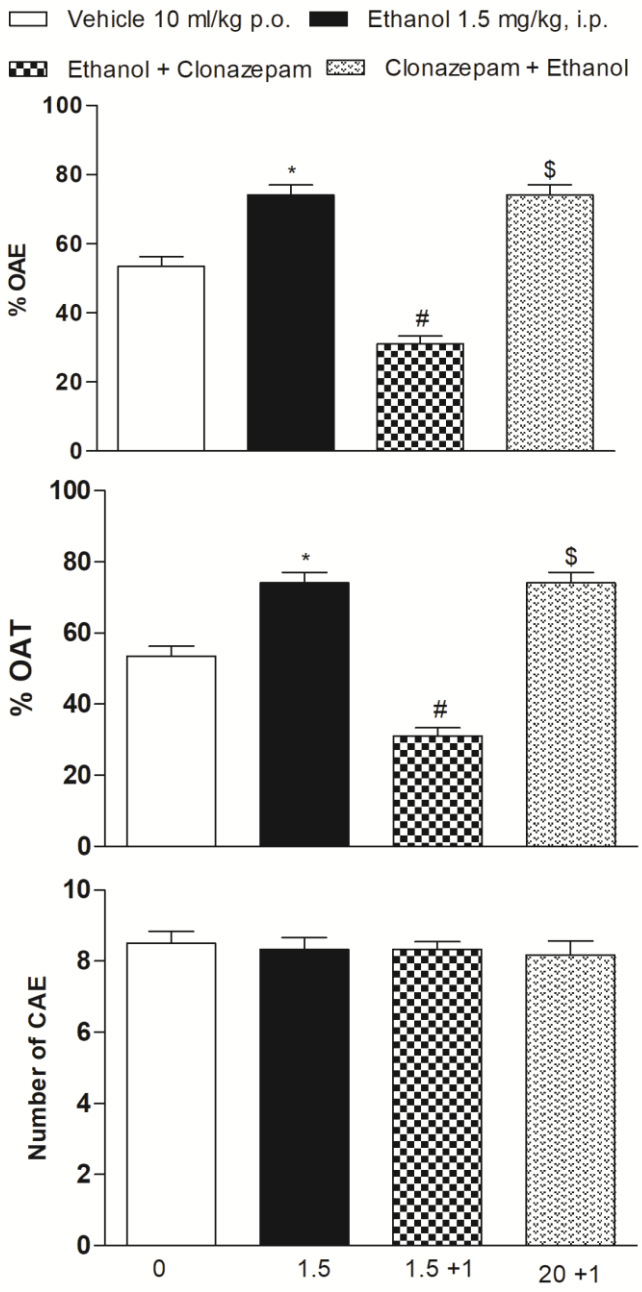
4.3. Effects of Clonazepam on Ethanol, Water, and Total Fluid Consumption

As shown in **Figure 3**, total fluid consumption was significantly influenced by treatment group ($F(2,18)=9.573$, $p=0.0015$), session ($F(6,108)=14.48$, $p<0.0001$), and group × session interaction ($F(12,108)=17.31$, $p<0.0001$). Mice receiving prolonged clonazepam treatment exhibited increased ethanol consumption accompanied by reduced water intake. All groups consumed significantly more ethanol than water throughout the experimental period ($p<0.05$).



4.4. Effects of Ethanol and Clonazepam on Anxiety-Like Behavior

As presented in **Figure 4**, analysis of Elevated Plus Maze performance revealed significant effects of arm type ($F(1,37)=231.68$, $p<0.0001$) and significant arm × treatment interactions. Clonazepam-treated mice spent significantly more time in the open arms and less time in the closed arms compared with vehicle-treated animals, indicating reduced anxiety-like behavior. No significant differences were observed in locomotor activity, suggesting that the anxiolytic effects were not associated with alterations in motor performance.



5. DISCUSSION

The present study demonstrates that chronic clonazepam treatment significantly modulates both ethanol consumption and anxiety-like behavior in Swiss mice. A notable finding was the biphasic effect of clonazepam on ethanol self-administration, characterized by an initial reduction in ethanol intake followed by a progressive increase during prolonged treatment. These findings suggest that the interaction between benzodiazepines and ethanol is dynamic and influenced by neuroadaptive changes occurring during chronic exposure.

The early reduction in ethanol self-administration observed following clonazepam treatment may be attributed to the shared pharmacological actions of clonazepam and ethanol on GABAA receptor-mediated neurotransmission. Both agents enhance inhibitory signaling within the central nervous system, thereby producing anxiolytic and sedative

effects. Consequently, acute clonazepam administration may partially substitute for the reinforcing and anxiolytic properties of ethanol, reducing the motivation to consume alcohol during the initial treatment phase. Similar findings have been reported by Licata and Rowlett (2008), who demonstrated that benzodiazepines and ethanol share overlapping neuropharmacological mechanisms through modulation of GABAA receptor function.

In contrast, prolonged clonazepam administration significantly increased ethanol self-administration and ethanol intake.

Chronic exposure to benzodiazepines has been shown to induce compensatory neuroadaptations, including alterations in GABAA receptor expression, receptor sensitivity, and downstream intracellular signaling pathways (Vashchinkina et al., 2014). These adaptive changes may contribute to the development of cross-tolerance between benzodiazepines and ethanol, thereby promoting increased alcohol consumption to achieve comparable pharmacological effects. Similar observations have been reported in experimental studies investigating long-term benzodiazepine exposure and alcohol-seeking behavior (Becker, 2012).

The significant positive correlation between ethanol rewards and blood ethanol concentrations confirms the validity of the operant self-administration model employed in the present study. This finding indicates that lever-pressing behavior accurately reflected ethanol intake and supports the reliability of the behavioral paradigm for assessing alcohol-directed motivation and reinforcement.

Analysis of fluid consumption revealed that the increase in total fluid intake during prolonged clonazepam treatment was primarily driven by enhanced ethanol consumption rather than water intake. This selective increase suggests that chronic clonazepam administration specifically altered the reinforcing properties of ethanol without affecting general drinking behavior. Such findings support the hypothesis that chronic modulation of GABAergic neurotransmission influences reward-related pathways associated with alcohol preference.

Behavioral assessment using the Elevated Plus Maze demonstrated significant anxiolytic-like effects of clonazepam, evidenced by increased open-arm exploration and reduced time spent in the closed arms. These observations are consistent with the well-established anxiolytic properties of benzodiazepines and corroborate previous reports demonstrating that positive modulation of GABAA receptors reduces anxiety-related behaviors in rodents (Walf and Frye, 2007). Importantly, locomotor activity remained unchanged among experimental groups, indicating that the observed behavioral effects were not secondary to sedation or motor impairment.

The relationship between anxiety and alcohol consumption is complex and bidirectional. Acute ethanol administration produces anxiolytic-like effects, whereas withdrawal following chronic exposure is associated with heightened anxiety and increased risk of relapse (Koob and Volkow, 2016). Therefore, the initial reduction in ethanol consumption observed following clonazepam treatment may reflect a decrease in anxiety-driven alcohol seeking. However, the subsequent increase in ethanol intake during prolonged treatment suggests the emergence of neuroadaptive mechanisms that override the initial anxiolytic benefits and promote alcohol-directed behavior.

In addition to GABAergic neurotransmission, both ethanol and benzodiazepines influence mesolimbic dopaminergic pathways involved in reward processing and reinforcement. Chronic activation of these circuits may alter dopamine signaling within the ventral tegmental area and nucleus accumbens, thereby enhancing the motivational properties of

ethanol (Volkow et al., 2017). Furthermore, adaptations in glutamatergic neurotransmission and stress-responsive neural circuits may contribute to the increased alcohol intake observed during prolonged clonazepam exposure.

Limitations and Future Perspectives

Despite providing important insights into the interaction between clonazepam and ethanol consumption, the present study has several limitations. First, only male Swiss albino mice were included, limiting the generalizability of the findings to female animals, where sex-dependent differences in alcohol consumption and anxiolytic responses have been reported. Second, the study relied primarily on behavioral assessments and did not evaluate the underlying neurochemical or molecular alterations associated with chronic clonazepam treatment. Third, only a single dose of clonazepam was investigated, preventing assessment of dose-dependent effects. Additionally, neurotransmitter levels, receptor expression profiles, and biomarkers associated with alcohol dependence were not measured. These limitations restrict mechanistic interpretation of the observed behavioral outcomes. Future studies should investigate the molecular mechanisms underlying clonazepam-induced alterations in ethanol consumption by examining changes in GABAA receptor subunit expression, dopaminergic neurotransmission, glutamatergic signaling, and neuroplasticity-related markers. Inclusion of both sexes and multiple dose levels would improve the translational relevance of the findings.

Moreover, assessment of withdrawal-associated behaviors, stress-related biomarkers, and neuroinflammatory pathways may provide a more comprehensive understanding of the interaction between chronic anxiolytic treatment and alcohol use. Advanced approaches such as immunohistochemistry, quantitative PCR, western blotting, and in vivo neurochemical analyses could further elucidate the neurobiological basis of the behavioral adaptations observed in the present study.

6. CONCLUSION

The present study demonstrates that chronic clonazepam treatment significantly influences ethanol consumption and anxiety-like behavior in Swiss mice. Acute clonazepam administration initially reduced ethanol self-administration and intake, whereas prolonged treatment resulted in a significant increase in ethanol consumption and preference.

Furthermore, clonazepam produced marked anxiolytic-like effects in the Elevated Plus Maze without significantly affecting locomotor activity, indicating that the observed behavioral changes were not attributable to alterations in general motor function.

These findings suggest that chronic modulation of GABAA receptor-mediated neurotransmission may differentially affect alcohol-directed behaviors over time. While the initial reduction in ethanol intake may reflect pharmacological overlap between clonazepam and ethanol, prolonged exposure appears to promote neuroadaptive changes that enhance ethanol-seeking behavior. The significant correlation between operant responding and blood ethanol concentrations further validates the self-administration paradigm used in this study.

Overall, the results highlight a complex interaction between chronic anxiolytic treatment and alcohol consumption and suggest that long-term benzodiazepine exposure may increase vulnerability to alcohol use–related behaviors. Further investigations employing neurochemical, molecular, and receptor-level analyses are warranted to elucidate the underlying mechanisms and their potential clinical implications for the management of anxiety disorders and alcohol use disorder.

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