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Effects of GABA Supplementation on Grooming Behavior and Social Interaction in a Propionic Acid-Induced Rat Model of Autism

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ABSTRACT

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by impaired social communication and repetitive behaviors. Propionic acid (PPA)-induced rodent models are commonly used to study ASD-like behaviors and evaluate potential therapies. This study investigated the therapeutic potential of gamma-aminobutyric acid (GABA) supplementation in mitigating PPA-induced behavioral deficits. Methods: Forty male Western Albino rats were divided into four groups: control, PPA-treated, GABA-treated, and PPA-GABA-treated. Behavioral assessments were conducted using the three-chamber social test to evaluate social interaction and repetitive behaviors. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. Results: PPA administration significantly impaired social interaction without causing significant changes in repetitive grooming behaviors compared to the control group, as evidenced by reduced time spent in the social chamber and increased time in the object chamber. GABA supplementation significantly improved social interaction, while causing a slight but non-significant increase in repetitive grooming behaviors. Conclusion: GABA supplementation demonstrated partial therapeutic effects in mitigating the social deficits induced by PPA administration in a rodent model of ASD. However, the observed increase in grooming behavior highlights the complex role of GABA in modulating ASD-like symptoms, suggesting the need for further investigation into its dual behavioral effects.

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by challenges in social communication and restricted, repetitive behaviors [1]. The etiology of ASD is multifactorial, involving a combination of genetic and environmental factors [2]. Globally, ASD affects approximately 1 in 100 children [3]. Despite its growing prevalence, the underlying causes of ASD remain unclear [4], and current therapeutic interventions are limited due to an incomplete understanding of the interplay between environmental factors and behavioral manifestations.

Animal models are indispensable for investigating the pathophysiology of ASD and evaluating potential therapies, as direct studies on human brain tissue are rarely feasible. Among the various environmental agents used to develop animal models, propionic acid (PPA) has emerged as a key tool for inducing behavioral and neuroinflammatory changes akin to those observed in ASD [5]. PPA, a metabolic byproduct of intestinal bacteria, can cross the gut-blood and gut-brain barriers, accumulate intracellularly, and cause acidification [6,7]. This process disrupts neurotransmitter functions [7], making PPA a widely adopted model for studying ASD-like behaviors and neuropathology [8-13]

Behavioral studies using PPA-induced rodent models have provided valuable insights into ASD-like symptoms, including social deficits, increased anxiety, and repetitive behaviors [14,15]. These models closely replicate the three core behavioral symptoms of autism: deficits in social interaction (e.g., three-chamber assay), impaired communication (e.g., ultrasonic vocalizations [USVs]), and repetitive motor behaviors (e.g., self-grooming or marble burying) [14]. Grooming, as a form of repetitive behavior, is frequently observed in humans and parallels self-grooming behaviors in animal models [16,17]. Additionally, self-grooming is recognized as a behavioral marker of stress and anxiety, as rodents often groom excessively in response to stressful stimuli [18].

Individuals with ASD are believed to experience higher levels of stress compared to typical individuals, due to challenges in adapting to changes, anticipation, sensory stimuli, and unpleasant events in their daily lives [19]. Stress can exacerbate anxiety, a common feature of ASD [20]. Stress-triggered grooming behavior in rodents involves specific neural circuits. A key example is a di-synaptic pathway connecting the hippocampal ventral subiculum, ventral lateral septum (LSv), and lateral hypothalamus tuberal nucleus. This circuit regulates grooming behavior with positive emotional significance, suggesting that grooming may play a role in reducing arousal after stress, providing an adaptive benefit [21].

Gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter, plays a crucial role in regulating neural development and function. Disruptions in GABAergic signaling have been associated with behavioral phenotypes of neurodevelopmental disorders, particularly autism [22]. Social processing challenges observed in autism are often linked to an imbalance in neurotransmitters, characterized by elevated levels of the excitatory neurotransmitter glutamate and/or reduced levels of inhibitory GABA [22].

This study aims to evaluate the effects of GABA on PPA-induced behavioral alterations, particularly social interaction and repetitive behaviors in a rat model of ASD. This research seeks to contribute to the development of more effective therapeutic strategies.

2. Materials and Methods

Animals

Forty young male Western Albino rats, approximately 3 weeks old and weighing between 60-80 g, were procured from the Experimental Surgery and Animal Laboratory at King Saud University, Riyadh, Saudi Arabia. The rats were housed in groups of five per cage under controlled conditions, maintaining a temperature of 22 ± 1 °C and a 12:12-hour light-dark cycle. They were provided with unlimited access to food and water. All experimental procedures were approved by the Ethics Committee for Animal Research at King Saud University, Riyadh (IRB No: KSU-SE-23-58).

Experimental Design

Forty rats were randomly divided into four groups, with each group consisting of ten rats. Group I (Control) received phosphate-buffered saline (PBS) orally for 24 days. Group II (PPA-intoxicated) was administered a neurotoxic dose of PPA (250 mg/kg body weight/day) for 3 days, followed by PBS for the remaining 21 days [7]. Group III (control-GABA) received PBS for the initial three days, then was orally treated with GABA supplementation (ABA Pure powder, NOW®, 200 mg/kg body weight/day) for 21

days, following the protocol outlined by Abd El-Hady et al. [23]. Group IV (PPA-GABA), referred to as the GABA-therapeutic group, received the same PPA dose as Group II, followed by GABA supplementation (Figure 1).

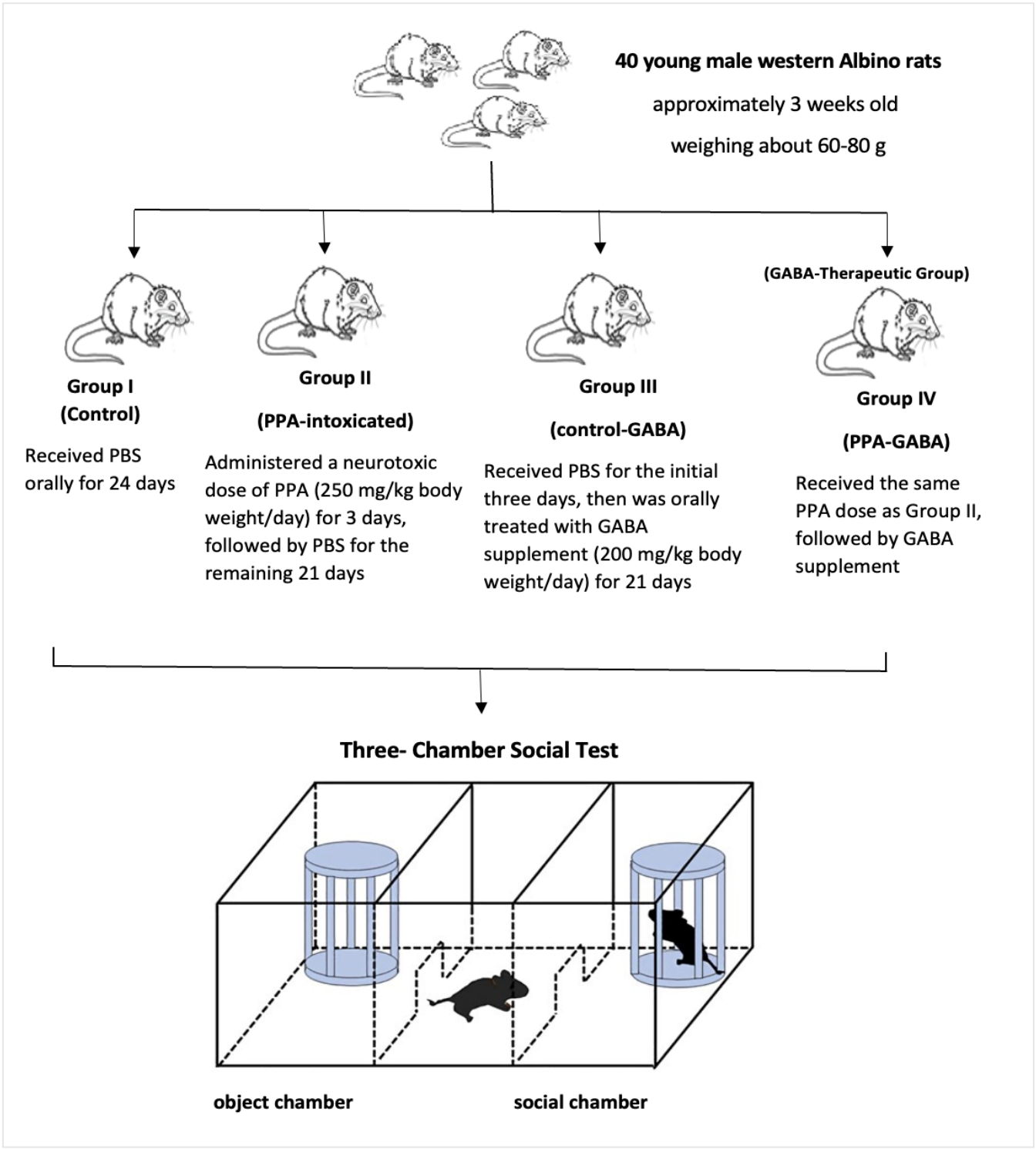


Figure 1: Diagrammatic scheme of experimental design

Social Interaction Behavioral Test

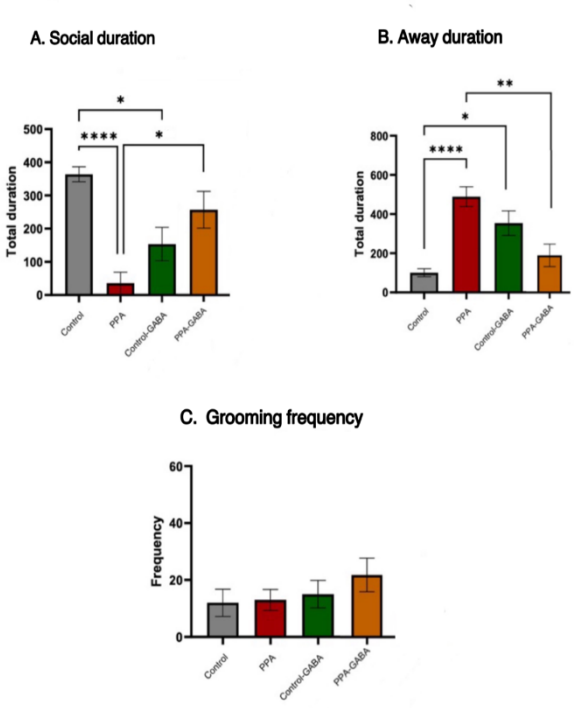
Social behavior was assessed using the three-chamber social test, a well-established method for evaluating social deficits in animal models of autism [24,25]. The test apparatus consisted of a clear plexiglass box measuring 80 cm × 40 cm × 40 cm, divided into three connected chambers with 15 cm × 15 cm doorways. Between trials, the apparatus was cleaned with 70% ethanol, wiped with paper towels, and left to air dry. To acclimate to the testing environment, animals were introduced into the testing room one hour before the experiment. Each rat was placed in the center chamber and allowed to explore freely for 5 minutes. Following this habituation period, a novel, same-sex conspecific rat of similar weight was introduced into one of the two perforated holding containers located in the side chambers. The test subject was then allowed to explore all three chambers for 10 minutes. To minimize side bias, the position of the conspecific rat was alternated between trials. The entire experiment was recorded using a Digital HERO camcorder (GoPro, San Mateo, California, USA), and the videos were analyzed using BORIS 7.9.16 software [26] by researchers blinded to the treatment groups. The time spent in each chamber relative to the total time was calculated. Grooming frequency was quantified as the number of occurrences of self-grooming, which involved the animal rubbing their forepaws on their face and licking or rubbing the rest of their body.

Statistical analysis

Prism version 9.1.1 was used for data analysis; the results were expressed as mean ± SE. One-way ANOVA, followed by Tukey's least significant difference (LSD) test for multiple comparisons. Differences were considered significant at **** $p < 0.0001$, *** $p < 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$.

3. Results

Figure 2 illustrates the effects GABA on social interaction and repetitive behaviors in the three-chamber social test across the four groups: control, PPA-treated, control-GABA and PPA-GABA. PPA-treated animals spent significantly less time in the social chamber than control group ($p < 0.0001$) and significantly more time in the object chamber ($P < 0.0001$), indicating impaired social behavior (Figure 2 A-B). PPA-GABA-treated animals demonstrated improved social behavior compared to the PPA group ($P < 0.05$), where they spent more time in the social chamber compared to the PPA-treated animals (Figure 2 A-B). Control-GABA-treated animals exhibited reduced social behavior indicated by the reduced time spent in the social chamber and more time in the object chamber compared to control animals ($P < 0.05$; Figure 2 A-B). Repetitive behavior assessed by



Grooming was not affected by PPA treatment, as grooming frequency was comparable between the control and the PPA-treated animals. PPA-GABA animals exhibited a slight increase in grooming frequency compared to the control and PPA-treated groups, though this difference was not significant.

Figure 2: Social interaction in the three-chamber social test following control (n = 7), propionic acid (PPA) treatment, (n = 7), control-GABA (n = 7), PPA-GABA (n = 7): (A) time spent in the social chamber relative to other chambers; (B) time spent in the empty (object) chamber relative to other chambers; (C) the number of grooming occurrences exhibited by focal animals. Data presented are means ± standard error. Significant one-way ANOVAs were followed by multiple comparisons by Tukey's least significance

difference **** $p < 0.0001$, *** $p < 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$.

4. Discussion

This study investigated the efficacy of GABA supplementation in mitigating PPA-induced autistic-like behaviors in a rat model, specifically highlighting notable improvements in social behavior.

PPA administration successfully induced behavioral deficits consistent with ASD, as evidenced by decreased time spent in the social chamber and increased time in the object chamber during the three-chamber social test. Supporting the role of PPA in autism, various administration methods have shown its ability to induce autism-like behavioral and physiological traits in rodent models [27].

In this study, the observation that the control-GABA group exhibited decreased social behavior. GABA is the primary inhibitory neurotransmitter in the central nervous system, and its modulation can influence various behaviors, including social interactions. For instance, Zhang et al. [28] demonstrated that increased cytosolic GABA levels due to a mutation of Aralar resulted in social behavioral deficits. This finding suggests that both insufficient and excessive GABA neurotransmitter levels negatively affect social behavior. The study highlights the importance of balanced GABAergic signaling.

On the other hand, regarding GABA's effects on sleep and relaxation, it is well-established that GABAergic transmission promotes sleep and has calming effects. For example, a study published in Foods demonstrated that fermented whey protein hydrolysate enriched with GABA enhanced sleep duration in mice by increasing brain GABA content. While these sedative properties are beneficial in the context of sleep, they could potentially contribute to decreased social interaction if heightened GABAergic activity leads to increased sedation or reduced arousal during social situations [29].

GABA supplementation following PPA treatment significantly increased the time spent in the social chamber and reduced the time spent in the empty chamber, highlighting its therapeutic potential in restoring inhibitory neurotransmission disrupted by PPA. This aligns with the established role of GABA as a key inhibitory neurotransmitter implicated in ASD pathophysiology [30]. Previous studies on GABA agonists, such as baclofen, have demonstrated their ability to significantly improve symptoms like hyperactivity, impaired social interaction, and spatial memory deficits in genetically modified mice [31,32]. Similarly, in mouse models with excitatory/inhibitory (E/I) imbalance, GABA_B receptor agonists, such as arbaclofen, have been shown to restore E/I balance and improve behavioral deficits [33].

The results presented in Figure 2 C show that grooming frequency is slightly increased in the PPA-GABA-treated group compared to both the control and PPA groups. This observed increase in grooming behavior aligns with findings from a study by Barros et al. [34] investigated the behavioral effects of antiepileptic drugs, such as topiramate, in the open field test and found that topiramate increased grooming frequency without impairing locomotor activity [34]. Topiramate has been shown to increase brain GABA levels [35], stimulate GABA-A receptor activity at non-benzodiazepine receptor sites and reduce glutamate activity at both AMPA and kainate receptors [36,37]. Therefore, the mechanism underlying this effect may be attributed to the GABA-related actions of topiramate, including the enhancement of GABAergic transmission and the suppression of excitatory pathways via its interaction with AMPA receptor sites. Its mode of action is multifaceted, with clinical observations revealing both positive (e.g., improvement in mood disorders) and negative (e.g., depression and psychosis) behavioral outcomes [38].

5. Conclusion

This study highlights the therapeutic potential of GABA supplementation in mitigating PPA-induced ASD-like behaviors in a rat model. GABA supplementation significantly improved social interaction and reduced time spent in the empty chamber, indicating its ability to restore disrupted inhibitory neurotransmission associated with PPA. However, an observed increase in grooming behavior suggests a dual role of GABA in modulating repetitive behaviors, which warrants further investigation. These findings emphasize the importance of targeting GABAergic pathways in developing effective therapies for ASD.

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