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NEUROBEHAVIORAL PROTECTIVE EFFECTS OF POTASSIUM IODIDE AGAINST POTASSIUM BROMIDE-INDUCED NEUROTOXICITY IN MICE

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ABSTRACT

Background: Potassium bromide (KBr) has long been used as an anticonvulsant agent; however, prolonged exposure may induce neurobehavioral disturbances associated with central nervous system depression. Potassium iodide (KI) is an essential iodine source required for normal neurological function, yet its potential protective effect against bromide-induced neurotoxicity remains poorly understood. **Objective:** This study aimed to evaluate the neurobehavioral effects of repeated potassium bromide administration in mice and to investigate the potential protective role of potassium iodide against bromide-induced behavioral alterations. **Materials and Methods:** Forty-eight adult male Swiss albino mice were randomly allocated into six experimental groups (n = 8/group). Animals received potassium bromide (90 mg/kg), potassium iodide (0.5 mg/kg), or their combinations three times weekly for 28 consecutive days using either distilled water or physiological saline as administration vehicles. Neurobehavioral performance was assessed using the Open Field test, Negative Geotaxis test, and Poking Head exploratory test. Data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test, with statistical significance accepted at $p \leq 0.05$. **Results:** Repeated potassium bromide administration significantly reduced locomotor activity and exploratory behavior, as evidenced by decreased crossed squares and rearing frequency in the Open Field test, prolonged Negative Geotaxis latency, and reduced head-dipping activity compared with the control group ($p \leq 0.05$). These behavioral impairments were most pronounced in mice receiving bromide dissolved in distilled water. Potassium iodide co-administration partially improved several behavioral parameters, although complete restoration to control values was not achieved. **Conclusion:** Repeated exposure to potassium bromide induced significant neurobehavioral impairment characterized by locomotor suppression, reduced exploratory activity, and impaired neuromotor coordination. Potassium iodide provided partial neurobehavioral protection, suggesting a modulatory effect against bromide-induced toxicity. Further investigations are warranted to elucidate the underlying mechanisms responsible for this protective interaction.

KEYWORDS: Neurobehavioral, Potassium Iodide, Potassium Bromide, Neurotoxicity, Mice.

INTRODUCTION

Potassium bromide (KBr) has long been recognized as an inorganic bromide salt with pharmacological activity, particularly because of its depressant effects on the central nervous system and its historical use as an anticonvulsant agent. However, repeated exposure to bromide may result in tissue accumulation and the development of bromism, a toxic state commonly associated with neurological manifestations such as ataxia, gait disturbance, impaired coordination, sedation, and behavioral suppression.[1,2] From a toxicological perspective, these manifestations are important because they indicate that bromide-induced toxicity is not limited to biochemical disturbance, but may extend to measurable functional impairment in motor and exploratory behavior.

Neurobehavioral assessment is therefore a sensitive experimental approach for detecting early functional alterations induced by neurotoxic compounds. The Open Field test is widely used in rodents to evaluate spontaneous locomotor activity, exploratory behavior, and anxiety-related responses.[3] In parallel, the Negative Geotaxis test provides an indirect measure of neuromotor coordination, postural reflex integrity, vestibular function, and motor responsiveness.[4] Moreover, exploratory head-dipping or poking behavior is commonly used to assess curiosity-driven exploration and behavioral reactivity to a novel environment.[5]

Accordingly, combining these behavioral endpoints provides a broader functional profile of bromide-induced neurotoxicity than relying on a single behavioral parameter.

Potassium iodide (KI), on the other hand, is primarily known for its physiological role as an iodine source required for thyroid hormone synthesis. Thyroid hormones are essential for normal brain development and neuronal function because they regulate neurogenesis, neuronal differentiation, synaptogenesis, myelination, and central nervous system maturation.[6,7] Therefore, disturbances in iodine availability may influence neurological performance directly through thyroid-related pathways. Importantly, bromide and iodide are halogen ions with potential biological interaction; experimental evidence indicates that increased bromide intake can alter iodine accumulation and metabolism in thyroid tissue, suggesting a competitive or interfering relationship between these ions.[8,9]

Despite the known neurological effects of bromide exposure and the recognized importance of iodine-dependent thyroid function in maintaining normal nervous system activity, the possible protective role of potassium iodide against potassium bromide-induced neurobehavioral impairment remains insufficiently investigated. This gap is particularly relevant because behavioral dysfunction may appear before overt structural damage, making functional tests useful early indicators of toxic interaction. Therefore, the present study was designed to evaluate the neurobehavioral effects of repeated potassium bromide administration in mice and to examine whether potassium iodide co-administration can attenuate these alterations using the Open Field test, Negative Geotaxis test, and Poking Head exploratory assessment.

MATERIALS AND METHODS

Experimental Animals

Forty-eight healthy adult male Swiss albino mice weighing 25–30 g were used in this experimental study. The animals were obtained from the Experimental Animal House and were housed under standard laboratory conditions at a temperature of 22 ± 2°C, relative humidity of 50–60%, and a 12 h light/12 h dark cycle. Animals had free access to standard laboratory chow and drinking water throughout the experimental period. Before initiating the experiment, all mice were acclimatized to the laboratory environment for one week.

Chemicals

Potassium bromide (KBr) and potassium iodide (KI) of analytical grade were used throughout the study. Fresh solutions were prepared immediately before administration using sterile distilled water or physiological saline (0.9% NaCl) according to the assigned experimental group.

Experimental Design

The mice were randomly allocated into six equal experimental groups (n = 8 per group) and treated three times weekly for 28 consecutive days.

- **Group I (Control):** received distilled water only.
- **Group II (KI):** received potassium iodide (0.5 mg/kg body weight).
- **Group III (KBr + NS):** received potassium bromide (90 mg/kg body weight) prepared in normal saline.
- **Group IV (KI + KBr + NS):** received potassium iodide (0.5 mg/kg) followed by potassium bromide (90 mg/kg) prepared in normal saline.
- **Group V (KI + KBr + DW):** received potassium iodide (0.5 mg/kg) followed by potassium bromide (90 mg/kg) prepared in distilled water.
- **Group VI (KBr + DW):** received potassium bromide (90 mg/kg) prepared in distilled water.

The experimental design was established to evaluate the neurobehavioral alterations induced by repeated potassium bromide exposure and to determine whether potassium iodide administration could attenuate these behavioral disturbances. In addition, the use of two different vehicles (normal saline and distilled water) enabled assessment of any potential influence of the administration medium on bromide-induced neurotoxicity.

Neurobehavioral Assessment

Behavioral evaluation was performed at the end of the treatment period by an investigator blinded to group allocation. All behavioral tests were conducted in a quiet room under identical environmental conditions, and the apparatus was cleaned with 70% ethanol between animals to eliminate olfactory cues.

Open Field Test

The Open Field test was used to evaluate spontaneous locomotor activity and exploratory behavior. Each mouse was individually placed in the center of the apparatus and allowed to explore freely for 5 min. The total number of crossed squares, rearing episodes, defecation pellets, and urination events were recorded.

Negative Geotaxis Test

Motor coordination and vestibular function were assessed using the Negative Geotaxis test. Each mouse

was positioned head-downward on an inclined plane (45°), and the time required to rotate 180° toward the upward direction was recorded in seconds. Three trials were performed for each animal, and the average latency was calculated.

Poking Head Test

Exploratory behavior was evaluated using the Poking Head test. Each mouse was allowed to explore the apparatus for 5 min, and the total number of head-dipping responses into the holes was recorded as an indicator of exploratory motivation.

Statistical Analysis

Data were analyzed using GraphPad Prism version XX (GraphPad Software, San Diego, CA, USA) (or SPSS version XX if applicable). Results are expressed as mean ± standard error of the mean (SEM). Statistical comparisons among groups were performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison post hoc test. Statistical significance was accepted at $\mathbf{p \leq 0.05}$.

RESULTS

Neurobehavioral Performance

Open Field Test

The effects of repeated potassium bromide administration, with or without potassium iodide co-treatment, on spontaneous locomotor and exploratory behavior are presented in **Table 1** and **Figure 1**. Significant differences among the experimental groups were observed in crossed squares and rearing frequency ($p \leq 0.05$), whereas defecation and urination did not differ significantly between groups.

Mice receiving potassium bromide prepared in distilled water (BR + DW) exhibited a marked reduction in locomotor activity, recording **58.5 ± 16.0** crossed squares compared with **76.5 ± 7.9** in the control group. A similar reduction was observed in the potassium iodide plus bromide distilled water group (I + BR + DW), which recorded **54.3 ± 13.3** crossed squares. Both groups were significantly different from the control and were classified under the same statistical subgroup (B), indicating impaired spontaneous locomotion following repeated bromide exposure.

A comparable trend was detected in rearing activity. The BR + DW group showed the lowest number of rearing episodes (**6.3 ± 3.5**), followed by the I + BR + DW group (**7.8 ± 2.3**), whereas the control animals demonstrated **12.3 ± 2.0** rearing events. These findings indicate reduced vertical exploratory behavior after repeated bromide administration.

In contrast, defecation and urination frequencies remained relatively stable across all treatment groups, with no statistically significant differences detected ($p > 0.05$), suggesting that autonomic behavioral responses were minimally influenced under the present experimental conditions.

Overall, repeated potassium bromide exposure predominantly affected locomotor and exploratory activities rather than autonomic behavioral parameters (Table1).

Table 1. Effect of repeated potassium bromide and potassium iodide administration on Open Field behavioral parameters in mice (Mean ± SEM).

Treatment Group	Crossed Squares	Rearing	Defecation	Urination
Control	76.5 ± 7.9 A	12.3 ± 2.0 A	0.3 ± 0.3 A	0.3 ± 0.3 A
KI	80.8 ± 16.4 A	15.8 ± 3.0 A	0.4 ± 0.3 A	0.4 ± 0.3 A
KBr + NS	72.3 ± 5.3 A	11.3 ± 3.4 A	0.2 ± 0.3 A	0.3 ± 0.3 A
KI + KBr + NS	70.5 ± 6.7 A	13.0 ± 3.1 A	0.3 ± 0.3 A	0.3 ± 0.3 A
KI + KBr + DW	54.3 ± 13.3 B*	7.8 ± 2.3 B*	0.5 ± 0.5 A	0.5 ± 0.3 A
KBr + DW	58.5 ± 16.0 B*	6.3 ± 3.5 B*	0.5 ± 0.3 A	0.5 ± 0.5 A

*Values are expressed as Mean ± SEM. Different uppercase letters indicate significant differences among groups (Tukey test, $p \leq 0.05$). * indicates significant difference versus the control group.*

Negative Geotaxis and Exploratory Head-Dipping

Motor coordination and exploratory behavior are summarized in **Table 2** and **Figure 2**.

Negative geotaxis latency differed significantly among the experimental groups ($p \leq 0.05$). The BR + DW group demonstrated the longest latency (**5.5 ± 1.3 s**), followed by the I + BR + DW group (**5.0 ± 1.3 s**), whereas the control group completed the task within **3.0 ± 0.9 s**. These findings indicate deterioration of neuromotor performance following repeated bromide administration.

Head-dipping behavior showed relatively similar values among most experimental groups. Nevertheless, mice treated with bromide in distilled water exhibited the lowest exploratory frequency (**12.0 ± 6.1**) compared with the control group (**21.3 ± 9.4**), indicating a significant reduction in exploratory motivation. Conversely, potassium iodide alone did not significantly alter exploratory behavior compared with untreated controls.

Collectively, the behavioral findings demonstrate that repeated potassium bromide exposure induced measurable neurobehavioral impairment characterized by reduced spontaneous locomotion, diminished exploratory

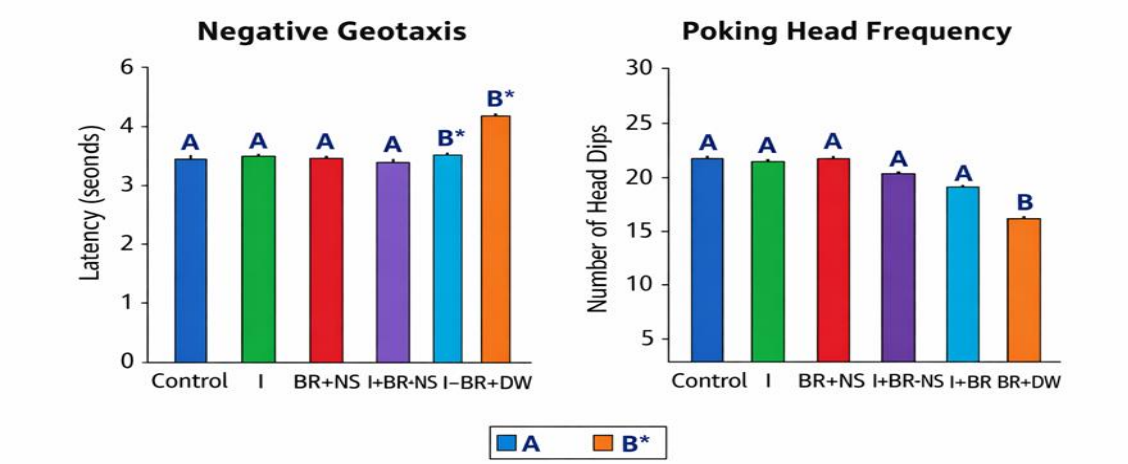
activity, and delayed neuromotor responses. Although potassium iodide co-administration produced partial improvement in several behavioral parameters, complete restoration to control values was not observed under the present experimental conditions.

As shown in Table 2 and Figure 2, repeated bromide administration significantly prolonged Negative Geotaxis latency in the BR + DW and KI + BR + DW groups compared with controls ($p \leq 0.05$). Exploratory head-dipping behavior was also significantly reduced in the BR + DW group, whereas potassium iodide alone did not alter behavioral performance. These findings demonstrate that repeated bromide exposure impaired both neuromotor coordination and exploratory activity, while co-administration of potassium iodide produced only partial behavioral improvement.

Table 2: Effect of repeated potassium bromide and potassium iodide administration on Negative Geotaxis and Poking Head behavior (Mean ± SEM).

Treatment Group	Negative Geotaxis (s)	Poking Head
Control	3.0 ± 0.9 A	21.3 ± 9.4 A
KI	3.0 ± 2.0 A	28.8 ± 6.4 A
KBr + NS	4.0 ± 1.5 A	23.0 ± 5.6 A
KI + KBr + NS	3.5 ± 1.9 A	24.5 ± 7.7 A
KI + KBr + DW	5.0 ± 1.3 B*	22.5 ± 3.7 A
KBr + DW	5.5 ± 1.3 B*	12.0 ± 6.1 B

Values are expressed as Mean ± SEM. Different uppercase letters indicate significant differences among groups (Tukey test, $p \leq 0.05$).



igure 2. Effect of potassium bromide and potassium iodide on Negative Geotaxis latency and exploratory head-dipping behavior in mice.

DISCUSSION

The present findings demonstrated that repeated potassium bromide administration significantly impaired locomotor performance and exploratory behavior, particularly in animals receiving bromide dissolved in distilled water. These behavioral alterations are consistent with the pharmacological properties of bromide ions, which depress neuronal excitability through enhanced inhibitory neurotransmission and altered membrane conductance. Chronic bromide accumulation has been associated with neurological manifestations including psychomotor slowing, muscular weakness, impaired coordination, sedation, and cognitive dysfunction, all of which may contribute to the reduction in spontaneous locomotor activity observed in the present study.[10,11]

The significant reduction in crossed squares and rearing frequency observed during the Open Field test suggests suppression of both horizontal and vertical exploratory activities. The Open Field paradigm is considered one of the most sensitive behavioral assays for detecting neurotoxic effects because locomotor activity depends on the functional integrity of multiple brain regions, including the cerebral cortex, basal ganglia, cerebellum, and hippocampus. Consequently, impairment in these behavioral indices is generally interpreted as evidence of functional disturbance within the central nervous system rather than isolated motor weakness.[12,13]

Interestingly, autonomic behavioral parameters, represented by defecation and urination frequency, remained statistically unchanged despite the marked decline in locomotor performance. This observation suggests that repeated bromide exposure selectively affected voluntary behavioral responses without producing generalized autonomic dysfunction. Similar findings have been reported in experimental

neurotoxicity studies, where locomotor suppression occurred in the absence of significant alterations in autonomic indices, indicating that behavioral impairment may precede broader neurological deterioration.[14]

Negative geotaxis performance was also significantly affected by bromide exposure. Animals receiving potassium bromide prepared in distilled water exhibited prolonged latency to reorient themselves against gravity, reflecting impaired neuromotor coordination and delayed vestibular reflexes. Since successful performance in the Negative Geotaxis test requires intact sensorimotor integration, cerebellar function, and vestibular processing, the prolonged latency observed in the present study indicates that repeated bromide administration adversely influenced neurological pathways responsible for postural control and coordinated movement.[15,16]

Exploratory head-dipping behavior exhibited a similar pattern, with bromide-treated mice demonstrating reduced exploratory motivation compared with control animals. Head-dipping is widely recognized as a behavioral indicator of environmental exploration and cognitive responsiveness. Therefore, the observed reduction may reflect central nervous system depression accompanied by diminished curiosity-driven behavior. Previous investigations have likewise demonstrated that toxic agents capable of depressing neuronal activity commonly reduce exploratory behavior before producing overt neurological deficits.[17]

An important finding of the present investigation was the partial improvement observed following potassium iodide co-administration. Although behavioral performance was not completely restored to control values, mice receiving potassium iodide generally exhibited less severe neurobehavioral impairment than animals treated with potassium bromide alone. This observation may be explained by the physiological interaction between bromide and iodide because both belong to the halogen family and may compete for transport and tissue distribution. Experimental evidence indicates that excessive bromide exposure interferes with iodine metabolism and decreases iodine availability within thyroid tissue, potentially disturbing thyroid hormone synthesis.[18,19]

The maintenance of adequate thyroid hormone production is essential for normal neuronal metabolism, synaptic transmission, axonal maturation, and myelin maintenance throughout life. Consequently, preservation of iodine availability by potassium iodide supplementation may indirectly support neuronal function and partially counteract bromide-induced neurological impairment. Nevertheless, the incomplete behavioral recovery observed in the present study indicates that bromide neurotoxicity is likely mediated through multiple mechanisms extending beyond alterations in iodine metabolism alone.[20]

Another noteworthy observation was the apparent influence of the administration vehicle. Animals receiving bromide dissolved in distilled water consistently exhibited greater behavioral deterioration than those receiving bromide in physiological saline. Although the precise mechanism remains uncertain, this difference may reflect altered ionic interactions between bromide and chloride ions. Because chloride competes with bromide during renal tubular reabsorption and systemic distribution, physiological saline may facilitate bromide elimination or reduce tissue accumulation, thereby attenuating its neurotoxic effects. However, this hypothesis requires confirmation through pharmacokinetic investigations specifically designed to quantify bromide distribution and clearance.[21]

Collectively, the present findings indicate that repeated potassium bromide administration induces significant neurobehavioral dysfunction characterized by reduced spontaneous locomotion, impaired motor coordination, and diminished exploratory behavior. Potassium iodide provided partial neurobehavioral protection, although it was insufficient to completely normalize behavioral performance under the current experimental conditions. These findings support further investigation into the interaction between bromide and iodide and suggest that modulation of halogen homeostasis may represent a potential strategy for reducing bromide-associated neurotoxicity.

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