

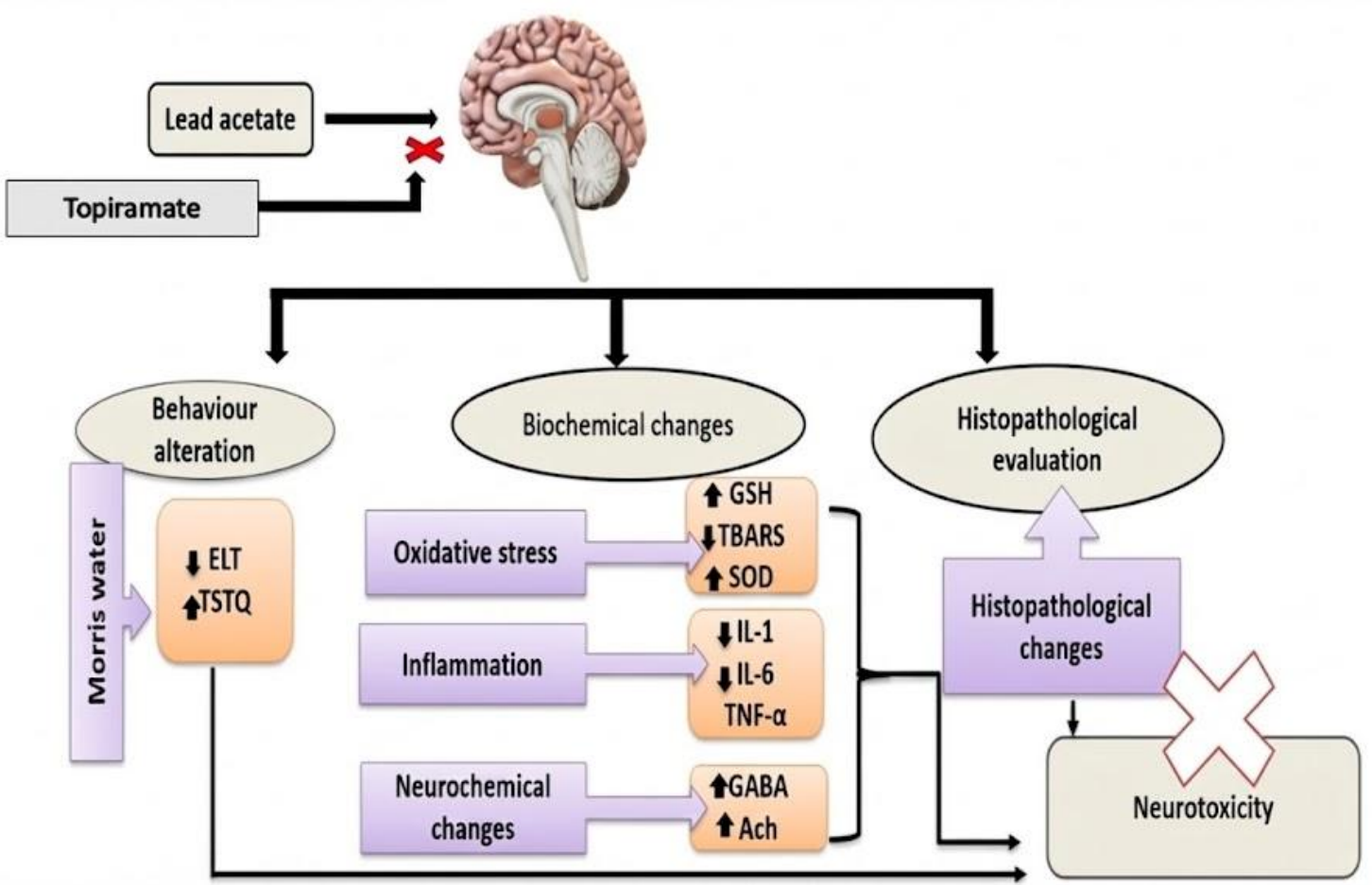
Neuroprotection in Lead Acetate-Induced Neurotoxicity Through Modulation of the GABAergic Pathway

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Key Takeaways

- Lead acetate induces cognitive impairment through oxidative stress, neuroinflammation, and disruption of cholinergic and GABAergic neurotransmission.
- Topiramate significantly improved memory and cognitive function in lead acetate-exposed rats.
- Topiramate restored neurotransmitter balance by increasing GABA and acetylcholine levels while reducing acetylcholinesterase activity.
- Neuroprotection was associated with reduced oxidative stress, inflammation, and neuronal damage.
- Picrotoxin reversed the protective effects of topiramate, confirming the involvement of the GABAergic pathway.
- Topiramate may represent a promising therapeutic strategy for environmental toxin-induced neurotoxicity and cognitive dysfunction.



INTRODUCTION

- Neurological disorders are characterized by progressive impairments in memory, cognition, and daily functional activities.
- Lead acetate, a widespread environmental neurotoxin, induces cognitive deficits by disrupting cholinergic and GABAergic neurotransmission.
- Lead exposure also promotes oxidative stress, neuroinflammation, and neuronal apoptosis, contributing to neurodegeneration.
- Topiramate, an antiepileptic drug with antioxidant, anti-inflammatory, and neuroprotective properties, has emerged as a promising candidate against lead-induced neurotoxicity.
- The present study investigated the neuroprotective efficacy of Topiramate against lead acetate-induced neurotoxicity and explored the involvement of the GABAergic pathway using Picrotoxin as a GABA-A receptor antagonist.

MATERIALS & METHODS

➤ **Experimental animals:** Wistar rats were randomly divided into 7 experimental groups.

➤ **Treatment protocol:** Animals received vehicle, lead acetate, topiramate (25 and 50 mg/kg), donepezil and picrotoxin (2.5 mg/kg).

➤ **Behavioral assessment:** Cognitive function was evaluated using the Morris Water Maze (MWM) test.

➤ **Biochemical analysis:** Brain tissue was analyzed for GABA, acetylcholine (ACh), acetylcholinesterase (AChE), oxidative stress markers, and pro-inflammatory cytokines.

Group	Treatment
Group I (Vehicle Control)	0.5% CMC (Vehicle), p.o., 14 days
Group II (Disease Control)	Lead acetate (40 mg/kg, p.o.), 14 days
Group III	Lead acetate (40 mg/kg, p.o.) + Topiramate (25 mg/kg, p.o.), 14 days
Group IV	Lead acetate (40 mg/kg, p.o.) + Topiramate (50 mg/kg, p.o.), 14 days
Group V (Standard)	Lead acetate (40 mg/kg, p.o.) + Donepezil (2.5 mg/kg, p.o.), 14 days
Group VI	Lead acetate (40 mg/kg, p.o.) + Picrotoxin (2.5 mg/kg, i.p.), 14 days
Group VII	Lead acetate (40 mg/kg, p.o.) + Topiramate (50 mg/kg, p.o.) + Picrotoxin (2.5 mg/kg, i.p.), 14 days

RESULTS

Table 1: Impact of various pharmacological interventions on Escape Latency Time (ELT)

Treatment	Day 11 ELT (Sec)	Day 14 ELT (Sec)
Vehicle Control group	110 ±3.32	40 ±3.13 ^a
Disease control group	108 ±3.04	79.5 ±3.45 ^{a,b}
Lead acetate + Topiramate 25mg /kg	107 ±2.71	58 ±3.44 ^{a,c}
Lead acetate + Topiramate 50mg /kg	110 ±3.0	49 ±2.43 ^{a,c,d}
Lead acetate + Donepezil	107 ±3.15	47 ±3.11 ^{a,c}
Lead acetate + Picrotoxin	111 ±2.54	81 ±2.16 ^a
Lead acetate + Picrotoxin + Topiramate 50mg /kg	105 ±3.32	77 ±3.32 ^{a,e}

Figure 1: Impact of various Pharmacological interventions on TSTQ (sec)

Figure 2: Impact of various Pharmacological interventions on brain lead levels.

Figure 3: Impact of various Pharmacological interventions on brain GABA and ACh levels.

Figure 4: Impact of various pharmacological interventions on brain TBARS, GSH, SOD and catalase levels.

Figure 5: Impact of various Pharmacological interventions on brain TNF-α, IL-1β and IL-6 levels.

CONCLUSION

- Topiramate significantly attenuated lead acetate-induced cognitive deficits, oxidative stress, neuroinflammation, and neuronal damage.
- Its neuroprotective effects were mediated, at least in part, through modulation of the GABAergic pathway, as evidenced by reversal with picrotoxin.
- These findings support the potential of topiramate as a promising therapeutic strategy for the management of lead-induced neurotoxicity.

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