The involvement of opioidergic and nitrergic systems on seizure threshold induced by pentylenetetrazole in cholestatic mice

Nastaran Rahimi[1,2], Hedyeh Faghir-Ghanesefat[1,2], Masoumeh Mafi-Ghazvini[1,2], Ahmad R. Dehpour[1,2*]

[1] Experimental Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran.

[2] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Introduction:

It is common knowledge that central neural transmission is affected by chronic liver diseases. Cholestasis results in some changes in behavior which include fatigue, cognitive dysfunction, mood disorders, and seizures. Alteration of endogenous opioids and nitric oxide (NO) levels are well recognized in patients who developed cholestatic liver diseases. Opioid antagonists have been documented in reversing cholestasis-induced pruritus. Endothelial NO synthase (NOS)-derived NO could be protective against liver diseases, whereas NO produced by inducible NOS (iNOS) is deleterious. Moreover, the role of both NO and opioid have been well documented in different models of seizures. The aim of this study, therefore, was to evaluate the contribution of opioidergic and nitrergic pathways in pentylenetetrazole-induced seizures following chronic irreversible cholestasis in mice.

Materials & Methods:

Seizures were induced by intravenous injection of pentylenetetrazole on day 5 after bile duct ligation (BDL). Non-selective inhibitor of nitric oxide synthase, L-NAME; selective iNOS inhibitor, aminoguanidine; selective nNOS inhibitor, 7-nitroindazole; and antagonist of opioid receptors, naltrexone were administered intraperitoneally to animals 5 days after BDL.

Data are expressed as the means ± SEM clonic seizure threshold for each experimental group. The one- or two-way analyses of variance (ANOVAs) followed by Post hoc Tukey's tests were used to analyze the data of seizures. A P-value less than 0.05 was defined statistically significant. All statistical analysis was done by the 24th edition of SPSS software.

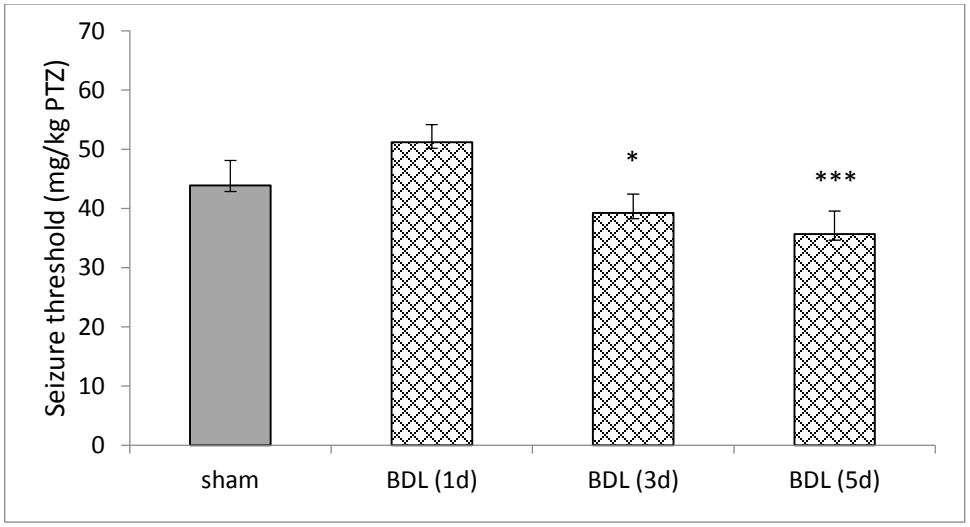
Results:

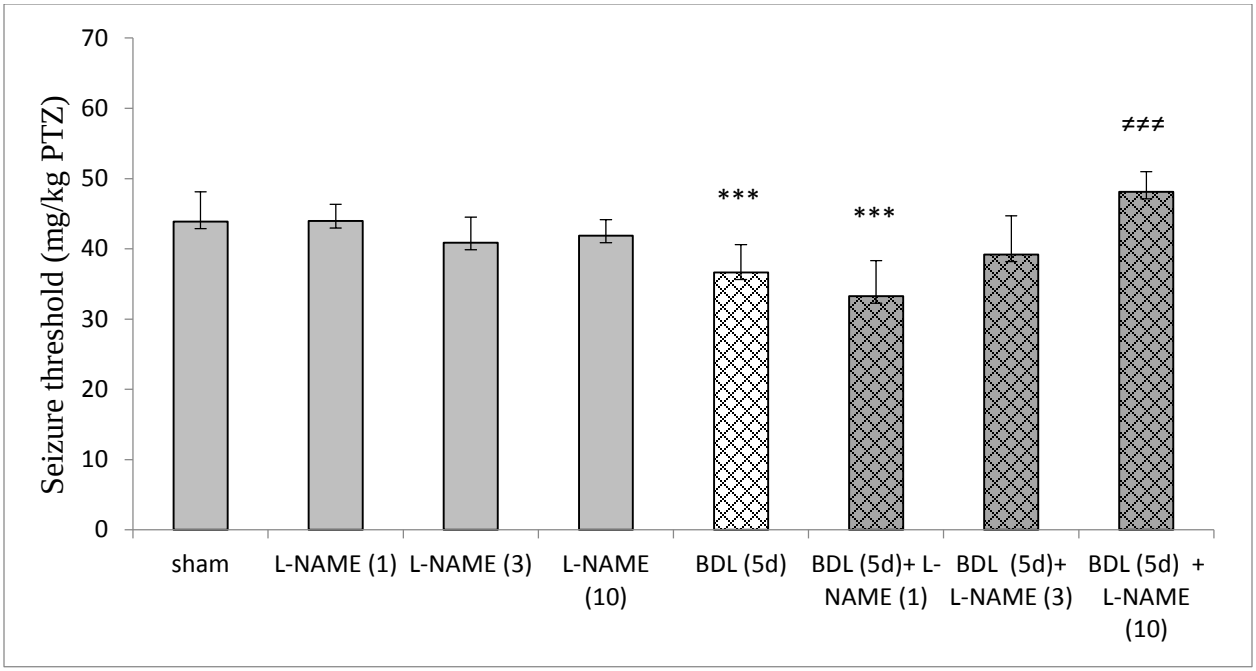
Seizure threshold significantly reduced in cholestatic mice in comparison to the sham group ($P < 0.001$). One- way ANOVA revealed that administration of L-NAME (10 mg/kg), aminoguanidine (50 mg/kg), naltrexone (10 mg/kg) and co-administration of L-NAME (3 mg/kg) and naltrexone (10 mg/kg) significantly reversed the pro-convulsant effect of bile duct ligation ($P < 0.001$). But, 7-nitroindazole did not alter the seizures threshold of cholestatic mice.

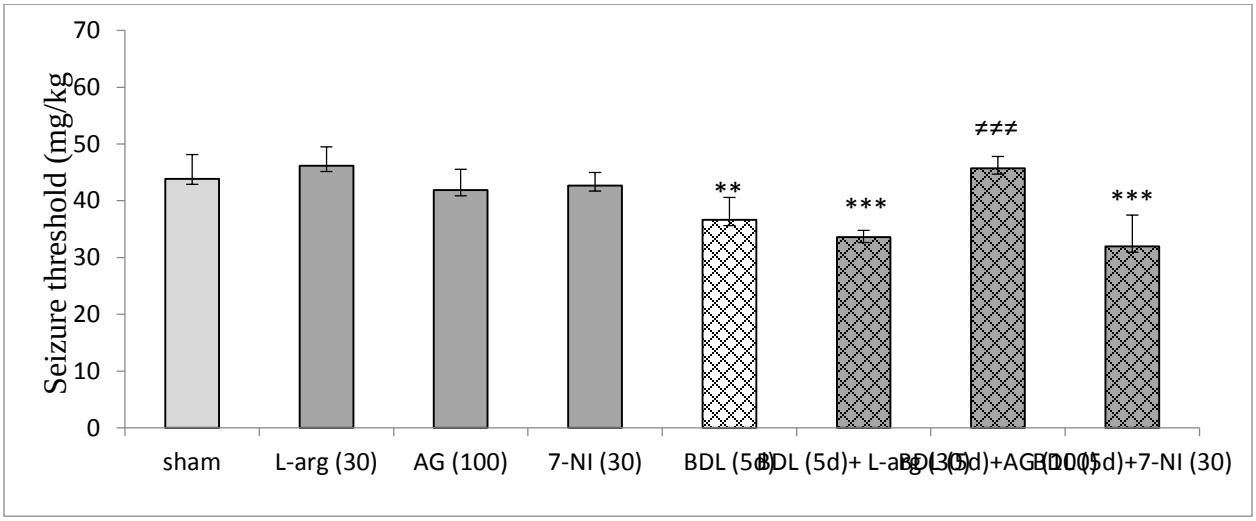
Conclusion:

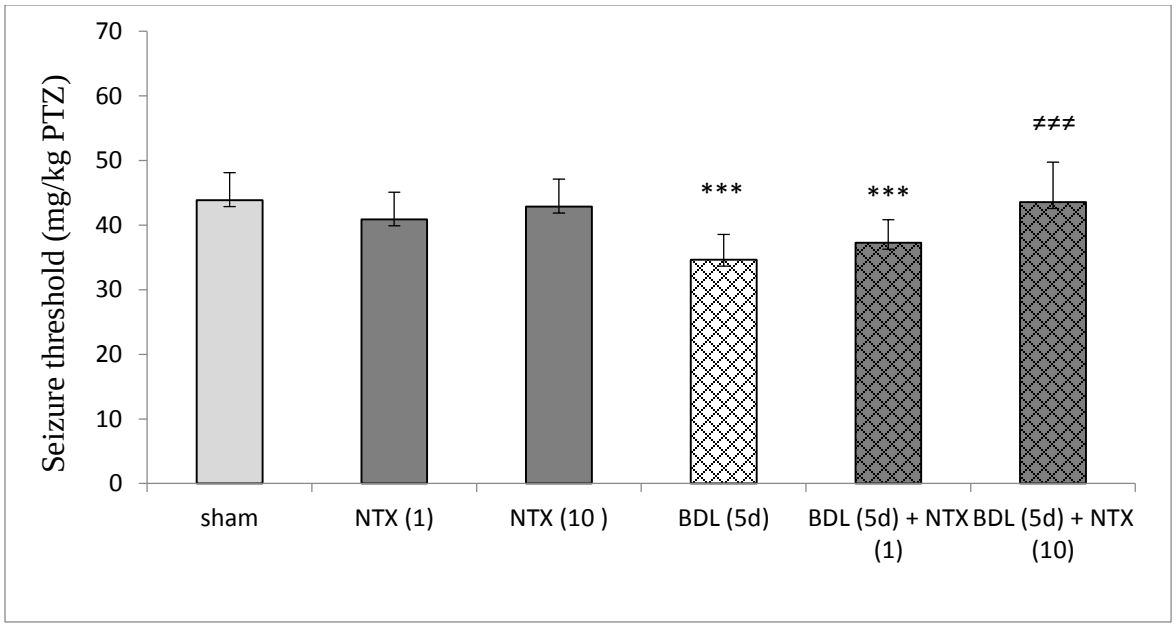
Our results suggest that inducible nitric oxide synthase and opioid receptor may be involved in cholestasis pro-convulsive property in mice.

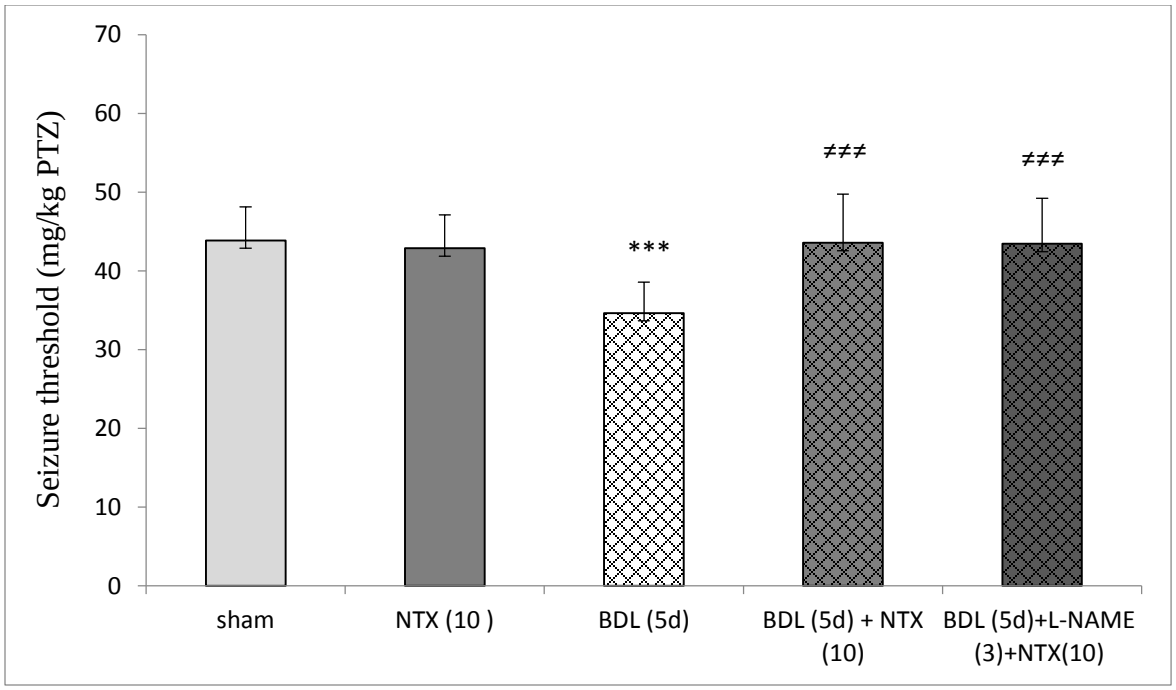
Figure:




Seizure threshold (mg/kg PTZ)
70
60
50
40
30
20
10
0
***
***
≠≠≠
sham
L-NAME (1)
L-NAME (3)
L-NAME (10)
BDL (5d)
BDL (5d)+ L-NAME (1)
BDL (5d)+ L-NAME (3)
BDL (5d) + L-NAME (10)


Seizure threshold (mg/kg
70
60
50
40
30
20
10
0
**
***
≠≠≠
***
sham
L-arg (30)
AG (100)
7-NI (30)
BDL (5d)
BDL (5d)+ L-arg (30)
BDL (5d)+AG (100)
BDL (5d)+7-NI (30)


Seizure threshold (mg/kg PTZ)
70
60
50
40
30
20
10
0
***
***
≠≠≠
sham
NTX (1)
NTX (10)
BDL (5d)
BDL (5d) + NTX (1)
BDL (5d) + NTX (10)


Seizure threshold (mg/kg PTZ)
70
60
50
40
30
20
10
0
***
≠≠≠
≠≠≠
sham
NTX (10)
BDL (5d)
BDL (5d) + NTX (10)
BDL (5d)+L-NAME (3)+NTX(10)