FIG. 1

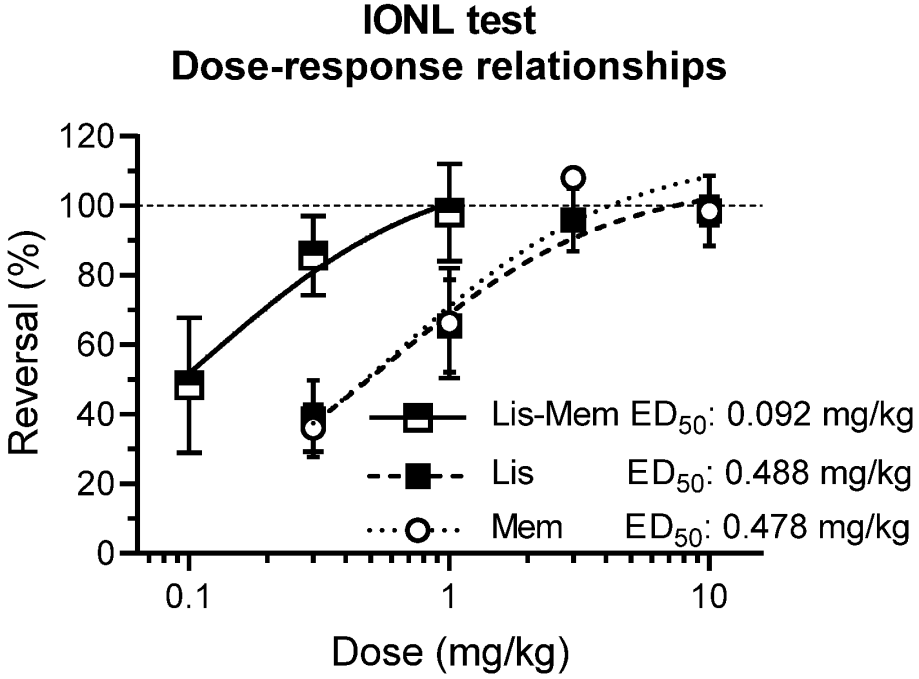

IONL test
Dose-response relationships
Reversal (%)
120
100
80
60
40
20
0
0.1
1
10
Dose (mg/kg)
Lis-Mem ED50: 0.092 mg/kg
Lis ED50: 0.488 mg/kg
Mem ED50: 0.478 mg/kg

FIG. 2

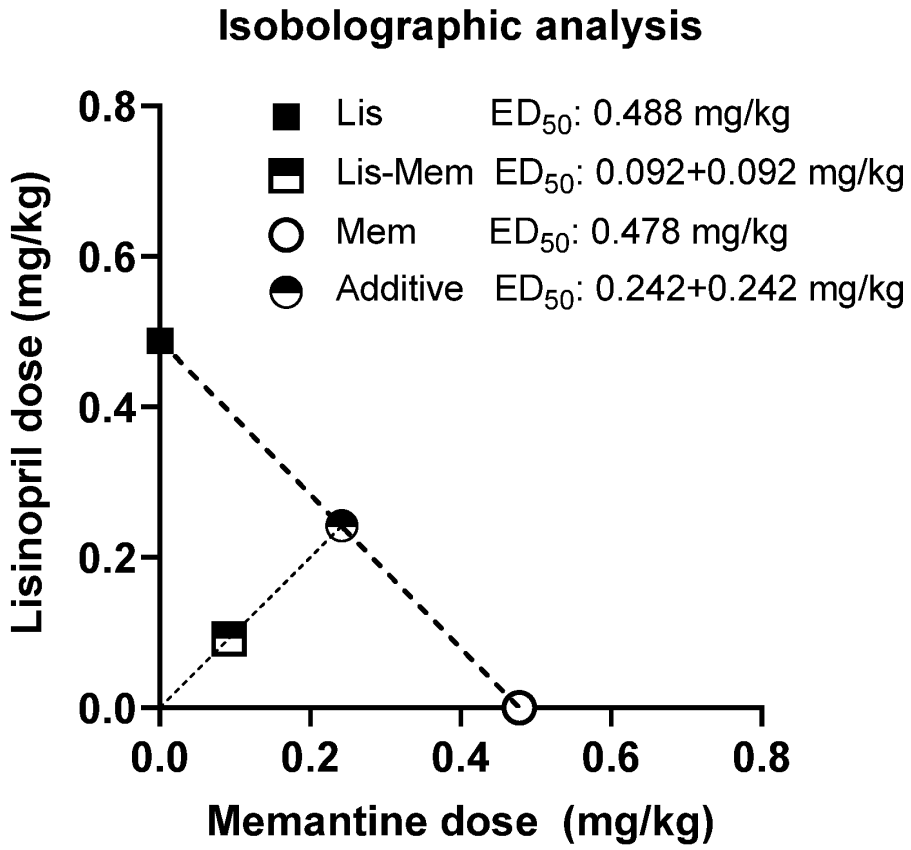
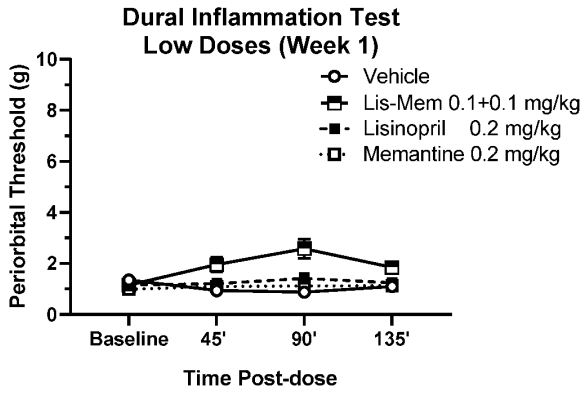
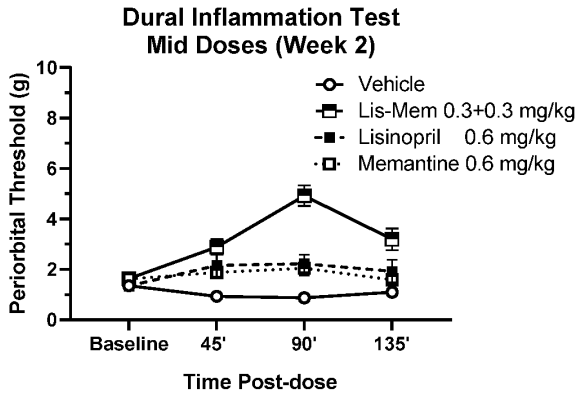

Isobolographic analysis
Lis ED50: 0.488 mg/kg
Lis-Mem ED50: 0.092+0.092 mg/kg
Mem ED50: 0.478 mg/kg
Additive ED50: 0.242+0.242 mg/kg
Lisinopril dose (mg/kg)
0.0
0.2
0.4
0.6
0.8
Memantine dose (mg/kg)

FIG. 3


Dural Inflammation Test
Low Doses (Week 1)
Vehicle
Lis-Mem 0.1+0.1 mg/kg
Lisinopril 0.2 mg/kg
Memantine 0.2 mg/kg
Periorbital Threshold (g)
0
2
4
6
8
10
Baseline
45'
90'
135'
Time Post-dose


Dural Inflammation Test
Mid Doses (Week 2)
Vehicle
Lis-Mem 0.3+0.3 mg/kg
Lisinopril 0.6 mg/kg
Memantine 0.6 mg/kg
Periorbital Threshold (g)
0
2
4
6
8
10
Baseline
45'
90'
135'
Time Post-dose

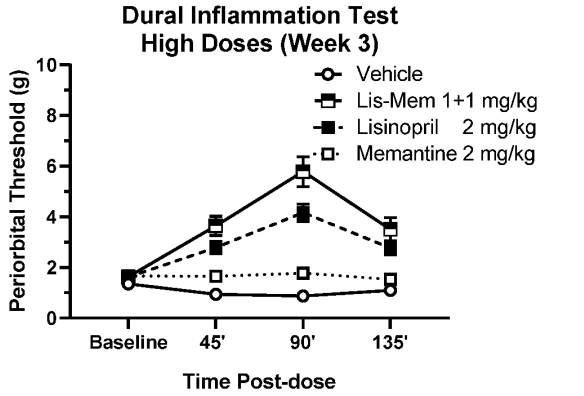

Dural Inflammation Test
High Doses (Week 3)
Vehicle
Lis-Mem 1+1 mg/kg
Lisinopril 2 mg/kg
Memantine 2 mg/kg
Periorbital Threshold (g)
0
2
4
6
8
10
Baseline
45'
90'
135'
Time Post-dose

FIG. 4

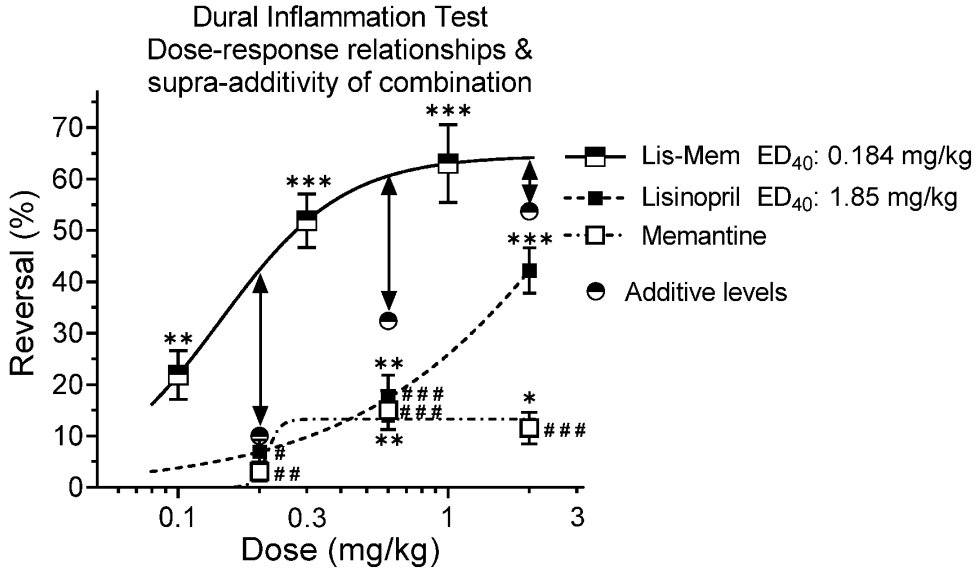

Dural Inflammation Test
Dose-response relationships &
supra-additivity of combination
Reversal (%)
Dose (mg/kg)
0.1
0.3
1
3
0
10
20
30
40
50
60
70
Lis-Mem ED40: 0.184 mg/kg
Lisinopril ED40: 1.85 mg/kg
Memantine
Additive levels

FIG. 5

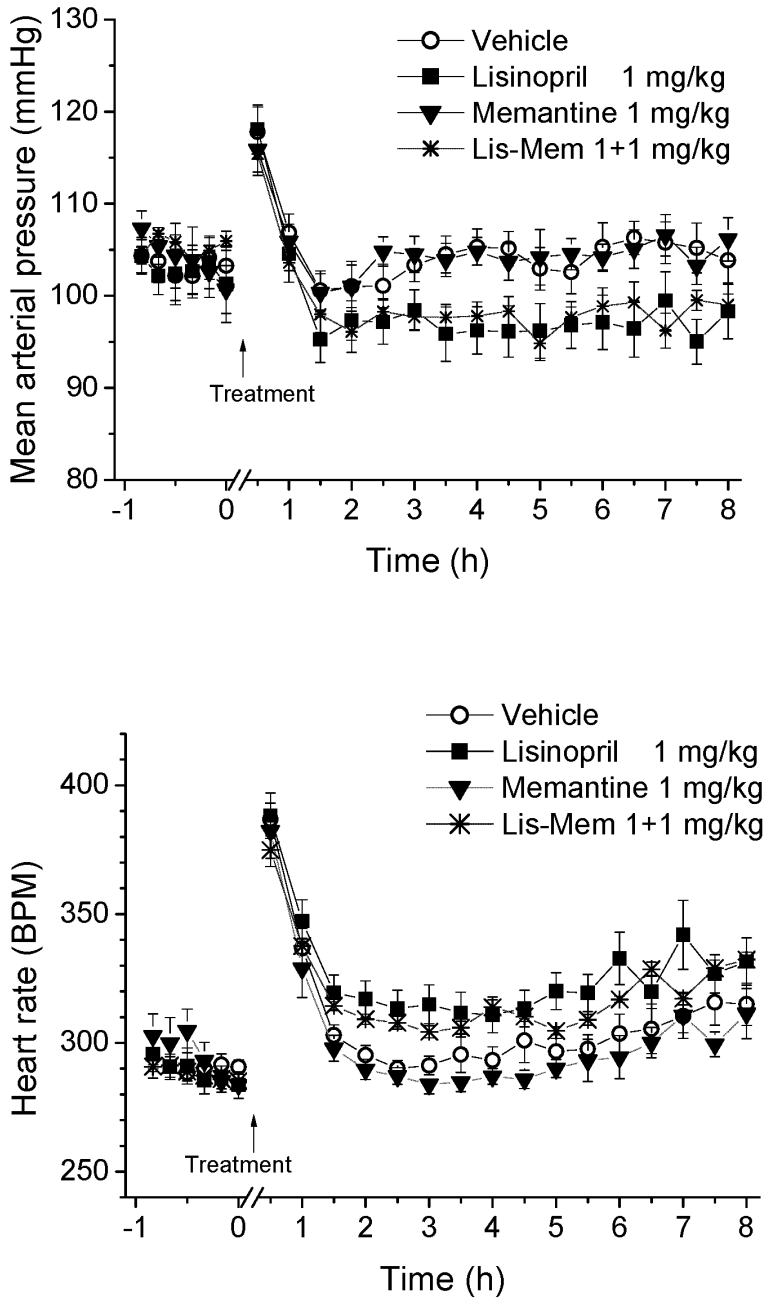

Mean arterial pressure (mmHg)
130
120
110
100
90
80
Vehicle
Lisinopril 1 mg/kg
Memantine 1 mg/kg
Lis-Mem 1+1 mg/kg
Treatment
-1
0
1
2
3
4
5
6
7
8
Time (h)
Heart rate (BPM)
400
350
300
250
Vehicle
Lisinopril 1 mg/kg
Memantine 1 mg/kg
Lis-Mem 1+1 mg/kg
Treatment
-1
0
1
2
3
4
5
6
7
8
Time (h)

FIG. 6

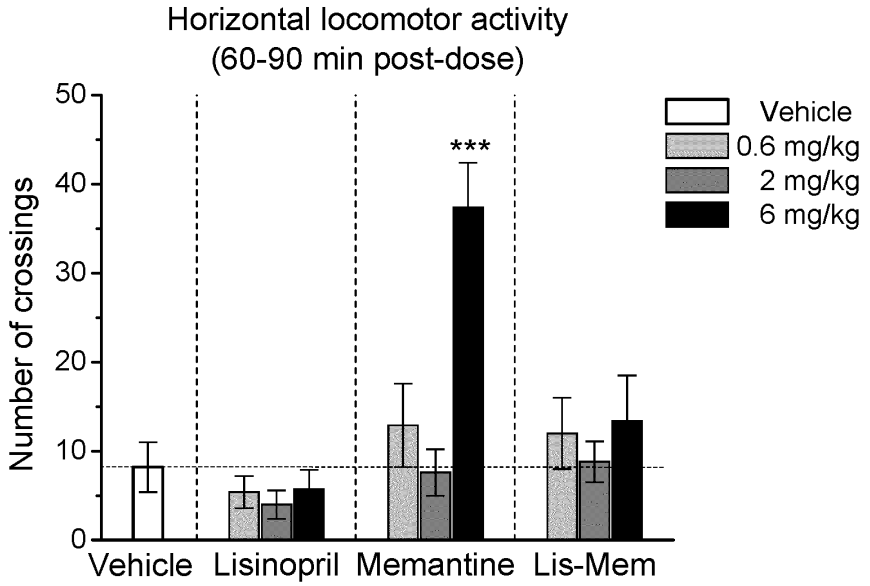

Horizontal locomotor activity
(60-90 min post-dose)
Number of crossings
50
40
30
20
10
0
***
Vehicle
0.6 mg/kg
2 mg/kg
6 mg/kg
Vehicle
Lisinopril
Memantine
Lis-Mem

FIG. 7

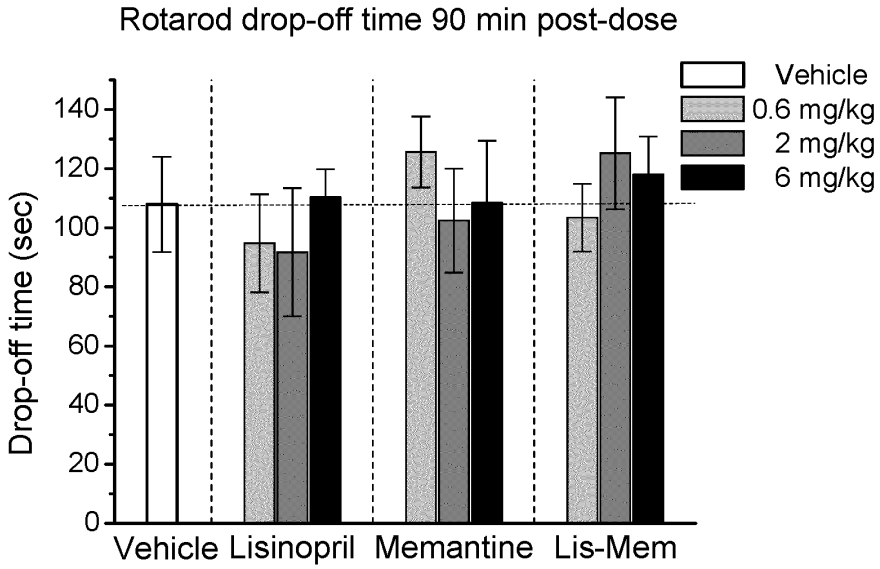
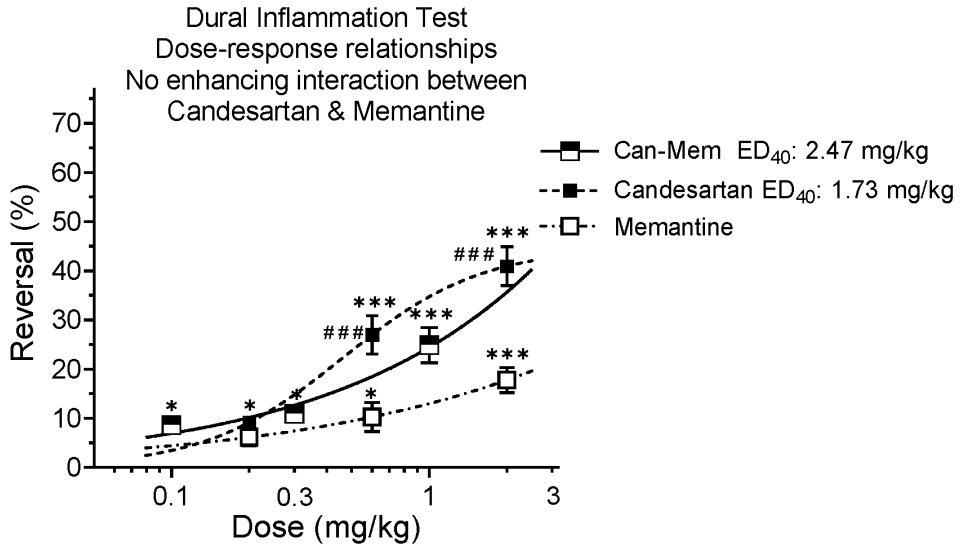

Rotarod drop-off time 90 min post-dose
Drop-off time (sec)
0
20
40
60
80
100
120
140
Vehicle
Lisinopril
Memantine
Lis-Mem
Vehicle
0.6 mg/kg
2 mg/kg
6 mg/kg

FIG. 8


Dural Inflammation Test
Dose-response relationships
No enhancing interaction between
Candesartan & Memantine
Reversal (%)
Dose (mg/kg)
0
10
20
30
40
50
60
70
0.1
0.3
1
3
Can-Mem ED40: 2.47 mg/kg
Candesartan ED40: 1.73 mg/kg
Memantine
*
*
*
*
***
***
***
***
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