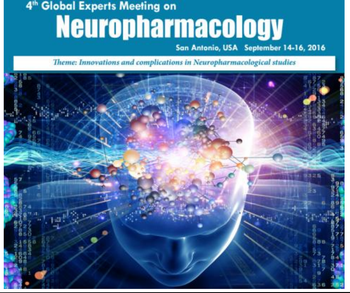

Effect of NMDA Receptor Antagonist and 5-HT$_{1A}$ Receptor Agonist on Behavioural Parameters In Serotonin Depletion Mice Model

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Background

Depression is the neurobiological disorder coupled with behavioural, neurochemical and physiological abnormalities (1). Central monoaminergic [5-Hydroxy tryptamine (5-HT), Dopamine (DA) and Nor-adrenaline (NA)] neurotransmitters contributes to the pathogenesis of depression (2). Dysfunction of 5-HT$_{1A}$ receptor has been recorded in the major depressive disorder (3).

Aim

The objective of the present work is that NMDA receptor antagonist and 5- HT$_{1A}$ agonist will restore brain serotonin levels and can have role in the treatment of depression.

Methods

Male *swiss albino* mice (25-30gms) were used in the study. 8-OH DPAT (5-HT$_{1A}$ agonist), memantine (non-competitive NMDA receptor antagonist were used in the study. Fluoxetine was used as a standard drug. To deplete serotonin, PCPA was administered.

Parameters studied

Depression, Anxiety and Cognitive functions.
Neurotransmitters and Neurochemicals in brain.
Interactive study with NMDA receptor antagonist memantine and 5-HT$_{1A}$ agonist 8-OH DPAT

Groups	Treatment	Dose
I	Control (0.9% NaCl, p.o)	1ml/kg
II	P-Chloro Phenyl Alanine (PCPA)*	300mg/kg followed by 100mg/kg for two weeks
III	Fluoxetine (Flx)+ PCPA*	20mg/kg
IV	Memantine (Mem) + PCPA*	20mg/kg
V	Memantine + PCPA*	40mg/kg
VI	8-OH DPAT (DPAT)+ PCPA*	0.2mg/kg
VII	8-OH DPAT + PCPA*	0.4mg/kg
VIII	8-OH DPAT + Memantine (Comb)+ PCPA*	0.2mg/kg + 20mg/kg

*PCPA - On first day 300mg/kg i.p. was administered followed by 100mg/kg for two weeks. On 8th day onwards behavioural parameters and cognitive function were assessed in the mice.

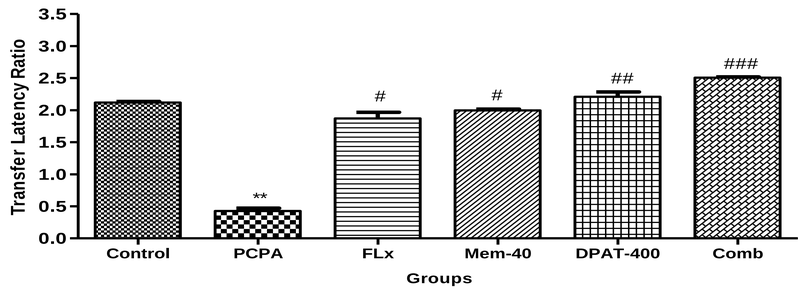
Results & Discussion

Drug Treatment	Time spent in central	Ambulations	Rearing frequency	Grooming Behaviour (sec)	Immobility Time (sec)
Control	26.67 ± 11.06	56.00 ± 10.41	12.83 ± 3.25	16.17 ± 2.99	44.50 ± 9.11
PCPA	5.33 ± 1.75***	15.67 ± 2.50***	24.67 ± 4.50***	26.33 ± 3.44***	176.25 ± 52.50***
Fluoxetine	20.00 ± 6.40##	25.33 ± 8.80	14.4 ± 3.78##	17.17 ± 4.45##	34.6 ± 13##
Memantine (20 mg/Kg) + 8-OH DPAT (0.2 mg/kg)	43.25 ± 6.56###	55.02 ± 5.39###	4.83 ± 1.83###	20.00 ± 3.03	44.80 ± 9.88###

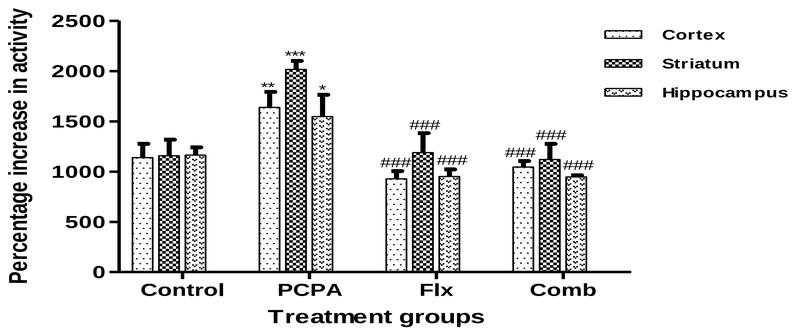
Table represents open field exploratory behaviour in PCPA treated mice. The values are expressed as mean ± SD. *** & ## and ### denotes statistical significance at (p<0.001) & (p<0.01) and (p<0.001) versus control and PCPA treated group respectively.

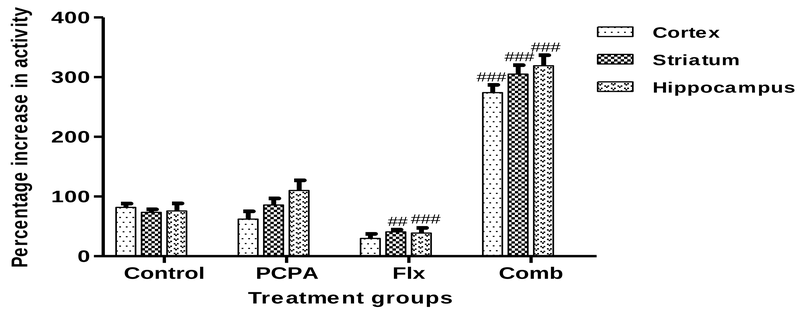
Drug Treatment	Immobility Time (Sec)	Total Swim Count	Active Swim Count
Control	127.50 ± 31.07	23.00 ± 6.33	10.50 ± 3.39
PCPA	220.25± 12.61***	7.21± 4.18**	1.67 ± 1.86
Fluoxetine	115.00 ± 21.46###	42.50 ± 12.29###	21.00 ± 8.65###
Memantine (20 mg/Kg) + 8-OH DPAT (0.2mg/kg)	43.25 ± 6.56###	55.02 ± 5.39###	4.83 ± 1.83###

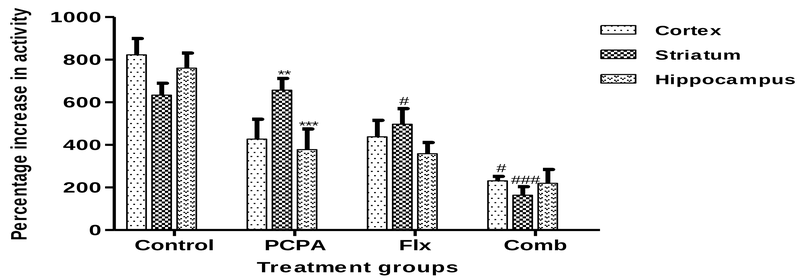
Table represents forced swim test behaviour in PCPA treated mice. The values are expressed as mean ± SD. *** & ** and ### denotes statistical significance at (p<0.001) & (p<0.01) and (p<0.001) versus control and PCPA treated group respectively.



The figure represents transfer latency ratio in PCPA treated mice in passive avoidance test. The values are expressed as mean ± SD. * & #, ## and ### denotes statistical significance at (p<0.5) & (p<0.05), (p<0.01) and (p<0.001) versus control and PCPA treated group respectively.







The graphs represent the effect of glutamate, aspartate and GABA in different regions of brain. The values are expressed in mean ± SD. *, ** and *** & # and ### denotes statistical significance at (p<0.05), (p<0.01) and (p<0.001) & (p<0.05) and (p<0.001) versus control and PCPA treated group respectively.

Effect of Metabolites in brain:

The combination therapy of memantine and 8-OH DPAT showed significant increase in the DOPAC and 5HT levels in brain stem in comparison to PCPA group.
In the other region, neurotransmitters level did not show any changes in comparison to PCPA treated group.

Conclusion

PCPA treated mice showed depression and anxiety. Memantaine and 8-OH DPAT showed antidepressant, anxiolytic activity in serotonin depleted mice. Memantine and 8-OH DPAT showed significant restoration in neurotransmitters level to normal. However, combination therapy did not show any additive or synergistic effects in PCPA treated mice.

References

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