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Original article

Effects of Administration of Perinatal Bupropion on the Population Spike Amplitude in Neonatal Rat Hippocampal Slices

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Abstract

Objective(s)
Bupropion is an atypical antidepressant that is widely used in smoke cessation under FDA approval. The study of synaptic effects of bupropion can help to finding out its mechanism(s) for stopping nicotine dependence. In this study the effects of perinatal bupropion on the population spike (PS) amplitude of neonates were investigated.

Materials and Methods
Hippocampal slices were prepared from 18-25 days old rat pups. The experimental groups included control and bupropion-treated. Bupropion (40 mg/Kg, i.p.) was applied daily in perinatal period as pre-treatment. Due to the studying acute effects, bupropion was also added to the perfusion medium (10, 50, 200 μM for 30 min). The evoked PS was recorded from pyramidal layer of CA1 area, following stimulation of Schaffer collaterals.

Results
A concentration of 10 μM bupropion had no significant effects on the PS amplitude. The 50 μM concentration of bupropion reduced the amplitude of responses in 50% of the studied cases. At a concentration of 200 μM, the recorded PS amplitudes were reduced in all slices (n= 22). Amplitude was completely abolished in 8 out of the 22 slices. The decrease of the PS amplitude was found to be more in the non-pre-treated slices than in the pre-treated slices when both were perfused with 200 μM bupropion.

Conclusion
The results showed the perinatal exposure to bupropion and its acute effects while indicating that at concentrations of 50 and 200 μM bupropion reduced the PS amplitude. It was also found that there was evidence of synaptic adaptation in comparison of bupropion-treated and non-treated slices whereas they were both perfused with 200 μM.

Keywords: Bupropion, Hippocampus, Population Spike, Rat, Slice

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Introduction

The perinatal effects of antidepressants on central nervous system due to its common usage are important issues in neuroscience researches. Bupropion, an atypical antidepressant, improves the rate of successful smoking cessation. Clinical observations have reported that bupropion had beneficial effects on mood and withdrawal symptoms in smokers who were not trying to quit (1). The mechanism(s) of action of bupropion have not yet been completely clarified, but its effectiveness in smoking cessation appears to be independent of its antidepressant properties (2). Bupropion is a nicotinic acetylcholine receptor antagonist (nAChR) across a similar concentration range as that it can inhibit synaptic dopamine and noradrenalin transporter functions. The combined action for inhibiting of these transporters and nAChR may provide a good pharmaceutical drug for depression and smoke cessation (3, 4). It has also been shown that bupropion has no significant affinity for various types of receptors such as α or β-adrenoceptors, 5-HT, and dopamine or nicotinic receptors. Bupropion is a weak, but relatively selective, inhibitor of dopamine (DA) reuptake. Its potency as an inhibitor of norepinephrine (NE) reuptake is one-half of that of DA (4, 5). Electrophysiological evidences have shown, the drug induced a dose-dependent attenuation of the spontaneous firing rate of norepinephrine and an increase in 5-HT firing neurons, without altering dopaminergic neurons of mesolimbic/cortical regions after sustained administration. Bupropion can increase extracellular dopamine and norepinephrine concentrations in mesocorticolimbic areas without influencing serotonin concentration (6-8). The mesolimbic dopamine neurons play a major role during the addiction process. Nicotine acts directly on ventral tegmental area (VTA), dopamine neurons as well as the synaptic inputs to these neurons. Mansvelder *et al* reported that pre-treatment of the brain slices with a clinically relevant concentration of bupropion decreases the effects of nicotine on DA neuron excitability (9). Nicotine is an addictive drug that has long-lasting and direct effects on synaptic functional in the hippocampus that may synergize with its effects on the ventral midbrain reward system (10). To advance our understanding of the therapeutic drugs for smoke cessation, we must seek a deeper understanding of cellular and molecular neurobiology as well as examining the function of relevant neural systems and extend our efforts in the effects of drugs on the pharmacology of the synapse. The knowledge of the cellular physiological responses of affected CNS neurons associates with changes of abuse drugs-induced is infancy. The previous focuses accomplished on alterations in cellular and synaptic plasticity in the VTA in response to addictive drugs (11-14). The synaptic plasticity can describe the mechanisms of nicotine addiction and learned associates within the context of tobacco usage. When a drug reduces nicotine dependency it also changes synaptic efficacy or synaptic plasticity. Over years of smoking, neuroadaptations occur and long term synaptic changes redound in the learned behaviors (15, 16). Bupropion is an important drug for smoke cessation so it can alter the efficacy of synapses. The population spike (PS) amplitude is a good parameter for the studying of synaptic efficacy. The changes in the PS amplitude can help to explain changes in the synaptic efficacy.

Some antidepressant drugs can affect LTP (long term potentiation) by changing the main features, such as PS amplitudes. Imipramine, desipramine and amitriptyline can block the induction of LTP in a concentration dependent manner (17). A study using treatment with fluoxetine (a selective serotonin reuptake inhibitor) reported that attenuation of LTP in the hippocampus dentate gyrus of the rats (18). Imipramine and (+) or (-) oxaprotiline had negligible effects on PS evoked by stratum radiatum stimulation. However, these two drugs can reduce postsynaptic excitability in low Ca^{+2}/ high Mg^{+2} medium after an exposure of more than 15 min (19). The aim of the present study was to assess the effects of perinatal bupropion exposure on synaptically evoked PS in the CA1 region of neonatal hippocampal slices.

Materials and Methods

Animals and Tissue preparation

All procedures were approved by Ethical Committee of Urmia University of Medical Sciences (Iran) and done while observing animal rights. Female Wistar rats (Animal Unit, Pasture Institute, Iran 180–200 g) were housed at an ambient temperature (22-25 °C) under a controlled 12 hr light /dark cycle (8.00-20.00) and had free access to standard food and tap water. Experimental groups included: (1) the control group in which pregnant rats received no pre-treatment; and (2) the treatment group which received bupropion hydrochloride daily (DiPharma, Italy, donated by Dr. Abidi, Pharmaceutical Laboratories of Iran). It was dissolved in saline solution and was administered intraperitoneally (i.p.) at a volume of 40 mg/kg during pregnancy and the nursing period (first day of pregnancy through to final pup dissociation). All administrations were performed between 08:00-10:00 hr. Briefly, rat pups between 18-25 days old were anaesthetized with ether and their brains were removed from the skull and were transmitted for 8-10 sec in a cooled artificial cerebrospinal fluid (ACSF at 4-6 °C) that was pre-bubbled with 5% CO_2, 95% O_2. Within 24 hr the last maternal injection, hippocampal slices were prepared from the rat pups according to standard protocols (20, 21) with a vibroslicer in thickness 400-450 μm (Campden Instruments UK, model MA752). The brain slices were immediately left to the holding chamber (Campden Instruments, model 745PID) for 1 hr to recover at room temperature (22-24 °C). ACSF was composed of (in mM): NaCl 125, KCl 2.5, $MgCl_2$ 1, $CaCl_2$ 2.5, Glucose 20, NaH_2PO_4 1, $NaHCO_3$ 25 (Merck, Germany), and pH= 7.3-7.4, osmolarity was 300±5 mosmol. Either a single slice or two slices were transferred into an interface recording chamber. They were then stabilized under a mesh and continuously submerged and superfused with carbogenated ACSF at 32±1 °C with the rate of 2 ml/min.

Experimental procedure

The positioning of the stimulation and recording electrodes was identified via light microscopy (×40). A borosilicate glass recording electrode was prepared using a microelectrode puller (Japanese, Narishige PC10) and filled with 1 M NaCl (resistance: 3-10 MOhm) used to detect PS in the stratum pyramidal cell layer of CA1 region. After electrode insertion, test stimuli were generated by stimulator (Bioscience. UK, CSF8173) and isolated by high current isolator (A385, WPI, USA). The input-output (I/O) curve was estimated at 50% of maximum synaptic response. After calculation curve, the PS were evoked by constant stimulation (duration 0.1 ms, 15 V) with an insulated bipolar tungsten electrode (tip diameter 0.05 mm) placed in the CA3 area of the Schaffer collateral pathway. Amplified signals digitized using a laboratory interface (ITC 16, Instrutech, Great Neck, NY, and USA) and then stored with Patchmaster (HEKA Electronic, Dr Schulze GmbH, Germany, ver 2.13) software on a Pentium IV PC. Recorded signals analyzed on-line with Patchmaster and off-line with Fitmaster (HEKA Electronic, Dr Schulze GmbH, Germany, ver 2.13). The responses were acquired and then bupropion was dissolved within ACSF solution at 10, 50 and 200 μM concentration and the slices were perfused for 30 min via changing the perfusion medium by means of three-way taps. At a constant flow rate of 2 ml/min, about 60 sec were required until the drug reached the recording chamber. Each slice was only used for one concentration. The evoked responses were recorded while bupropion was present and then the perfusion solution was changed to normal (drug-free) ACSF again. The responses were recorded via the previously stated methods for another 240 min.

Statistical analysis

The evoked response parameters of percent PS amplitudes were measured before and after perfusion of bupropion. Data were normalized and the mean±SEM of n trials are shown. In each slice, amplitude of PS after perfusion was measured by using one way-repeated measured ANOVA and the Wilcoxon matched pairs signed rank test. Significant different points between amplitudes with interval of five min after perfusion related to before perfusion were

analyzed and different points revealed. Adjustment values after perfusion identified and average values between different slices were analyzed by using ANOVA (post hoc - Tukey test) and correlated paired t-test. Also, Igor (ver 6.3, Wave metrics Inc USA) and GB-State (ver 5.0, Dynamic Microsystems, Inc USA) were used for data analysis.

Results

The results showed that concentration of 10 µM did not reduce the PS amplitudes (n= 7). Bupropion had negligible effects on PS evoked by stratum radiatum stimulation. When using at concentration of 50 µM and 30 min, the amplitudes were reduced in 50% of the cases (n= 8), average point to point showed that the perfusion bupropion could reduce evoked PS amplitude by 25%. Amplitude of PS reduced in the all treated slices (n= 22) which were perfused at 200 µM concentration of bupropion. Amplitude of PS was reduced in 8 out of 22 slices to 100%, that is, the amplitude was abolished. Reduction of PS amplitudes was reversible during a wash out of 30 min at 200 µM bupropion perfusion (n= 20, all slices= 22). In this group, average point to point showed that evoked PS amplitude was reduced by 65%. Using ANOVA test showed significant difference in PS amplitude comparison between these groups, the control group related to treated groups with perfusion at 50 µM of bupropion ($P< 0.05$) and at concentration of 200 µM ($P< 0.01$) (Figure 1). The amplitude of PS in the control group was fitted for baseline 100%. Perfusion at 200 µM of bupropion in the control (n= 15) and the bupropion pretreatment (n= 22) groups reduced the PS evoked responses. Changes of the PS amplitude are shown in Figure 2. Statistical comparison of PS amplitude by using repeated measurement ANOVA showed $F_{2,\ 143} = 453/3$, and average PS amplitudes had difference ($P< 0.0001$). There is a significant difference between analogous points from the two groups according to the Willcoxn rank sum/Mann-Whitney u-test ($P< 0.0001$). Average statistical comparison in two groups by separated variance t-test showed that the averages of inner group had significant difference ($P= 0.0002$).

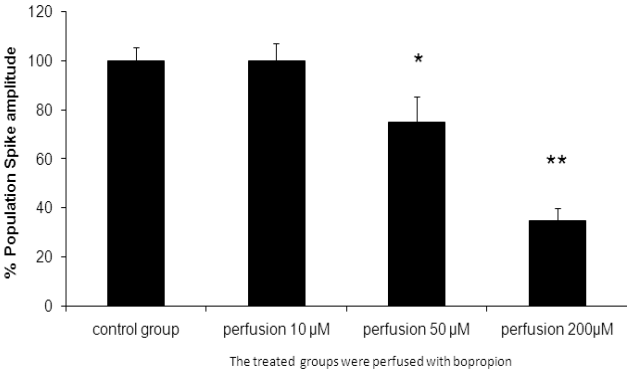

Figure 1. Comparison of the PS amplitude changes between the treated groups and control group. Amplitude of PS in the control group was fitted as 100%. Significant difference with the control group * $P< 0.05$; ** $P< 0.01$; ANOVA.

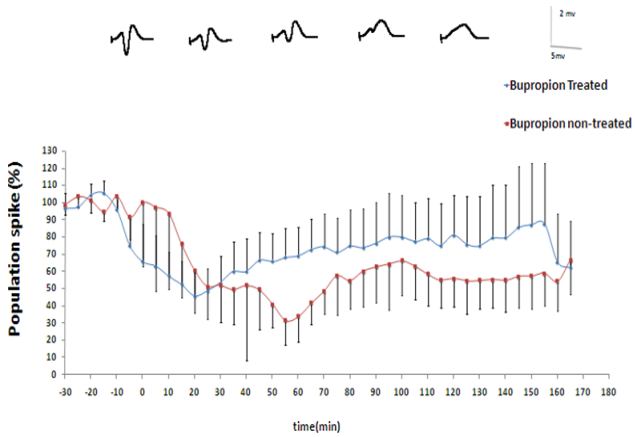

Figure 2. Changes of average PS amplitude in bupropion-treated and non-treated slices which were both perfused with bupropion (200 µM). Amplitude of PS before bupropion perfusion was fitted as 100% for baseline. Records were taken every five min, first 5 records are related to before perfusion and bupropion perfusion starting at initial time for 30 min. Upper traces show changes of population spike in the control group slice. $p< 0.0001$; according to the Wilcoxon Rank Sum/Mann-Whitney u-test compared to analogous points from two groups.

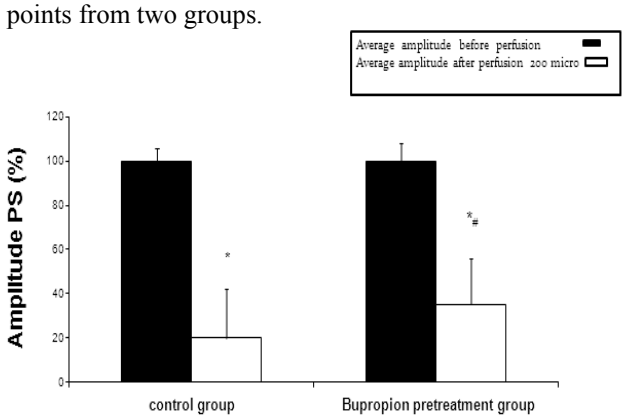

Figure 3. Comparison of PS amplitude changes in the treated and control groups which were both perfused with 200 µM bupropion, *$p< 0.05$ comparison before perfusion in each group. #$p< 0.05$ comparison after perfusion related to the control group.

The decrease of PS amplitude in the control group was more than perinatal treated group (Figure 3). The control group showed decreased amplitude by 80% and with more samples had their amplitude abolished, but in the treated group there was 65% decrease and only 8 out of the 22 slices had their PS amplitude abolished.

Discussion

Massicotte *et al* found that chronic administration of trimipramine (tricyclic antidepressant) caused a large reduction in the magnitude of LTP inducted in rats (22). Langosch and Walden found that acute trimipramine can decrease amplitude of PS dose dependently in guinea pig hippocampal slices (23). In this study, the authors found similar effects using bupropion. It was found that bupropion treatment of perinatal caused a subsequent decrease and potential abolishment of the PS of the synaptically evoked response in rat hippocampal slices. The decrease of the PS amplitude in non-pre-treated slices was more than that of the treated slices when they were both perfused with a 200 μM concentration of bupropion.

The molecular mechanism(s) responsible for the antidepressants induced neuroplastic changes in the hippocampus circuits are not fully understood. Different neuronal pathways may cause chronic effects of antidepressant drugs in the hippocampal synaptic plasticity. However, excitatory amino acid receptors, corticosteroids levels, monoamine neurotransmitters, cAMP response element binding protein (CREB), neurotrophic factors and other cellular messengers all have the potential to interact with a consequence for neuronal connectivity in the hippocampus. Antidepressant administrations can evaluate brain-derived neurotrophic factor (BDNF) levels, probably via noradrenaline and serotonin receptors (24-26). Neurotrophic effects of antidepressant drugs could help to restore the neuronal connectivity by inducing neurogenesis and new neural circuits, however, they facilitated synaptic connectivity (24, 27). It is obvious that antidepressant administration has the potential to change excitatory amino acid mediated synaptic plasticity and related to molecular and cellular organization in the brain (24). Long term antidepressant administrations may also lead to a sustained alteration in the intracellular signal transduction cascades which mediate the functions of G-protein-coupled receptors and which influence receptor desensitization (28). One of the molecular adaptation induced by antidepressant treatments in the strength of synaptic transmission in the hippocampus, was accomplished by the major mediator of synaptic plasticity: NMDA receptor.

Chronic administrations of imipramine or citalopram demonstrated to produce regional specific changes in expression of transcripts for N-methyl-D-aspartate receptor (NMDAR) subunits; also, it has been proposed that the ratio of NR2A / NR2B of NMDA receptor subunit controls the threshold for synaptic modifications by controlling Ca^{+2} entry and intracellular signaling cascades. Although regulation of the NR2A / NR2B ratio is clearly a more important determinant of the attribute synaptic efficacy but it is certainly only one of several important factors that affect the developmental and experience-dependent attribute of synaptic efficacy (29). The effects of bupropion on expression of transcript for NMDA receptor subunits and in the strength of synaptic transmission are unknown. It is possible that changes in brain gene expression, which are elicited after chronic bupropion treatments, might underlie the drug induced neural plasticity related to with its clinical efficacy in smoke cessation.

Bobula *et al* reported that treatments with imipramine or citalopram induced a reduction in the amplitude ratio of pharmacologically isolated AMPA/kainate to NMDA receptor-dependent components of field potentials. This occurred when they were evoked in layer II/III by stimulating of their underlying sites in layer V and was reduced the glutamatergic synaptic transmission in the cerebral cortex (30). The antidepressant administrations induce regulation of hippocampal synaptic neurotransmission by alteration of monoaminergic pathways projecting to the hippocampus (31). The level of synaptically released glutamate may change due to

antidepressants induced neuroadaptations changes in the presynaptic monoamine heteroreceptors located on glutamatergic terminals and/ or in the postsynaptic monoamine receptors (28). Bupropion, a nicotinic acetylcholine receptor antagonist, is able to inhibit nAChRs in soma and dendrite of pyramidal and interneuron cells. It also affects GLU/GABA release. The balance of these two neurotransmitters can influence synaptic efficacy. Intracellular calcium level regulates by excitatory amino acid receptors and it's determining synaptic responses such as evoked PS. It may be that antidepressant functional modulates this process in a number of ways, acting acutely through rapidly responsive excitatory amino acids systems, and chronically by inducing long term sustained changes in the cellular structure of hippocampus (32). Langosch and Walden suggested that the calcium antagonistic effects of Trimipramine may be responsible dose dependently for the inhibition of LTP and decrease PS amplitude as well as for its antidepressant action (23). Hippocampal configuration of GABAergic inhibitory interneuron has a major role in the synchronization of neuronal functional and is involved in the generation of large-scale network oscillations and has a direct influence on the integration of synaptic signals in the pyramidal cell (33). Bupropion may influence PS through interneurons. It seems likely that perikaryal synapses or interneurons could make the responses.

At higher doses, the atypical antipsychotic clozapine inhibits the Schaffer-collateral evoked field potentials in the hippocampal slices (34). Acute clozapine also enhances the NMDA-mediated of glutamatergic synaptic responses in the striatal and the prefrontal cortex (PFC) slices and field potential responses potentiates in the hippocampus *in vivo*. In clozapine, the long-lasting potentiation of the NMDA component of evoked glutamatergic excitatory postsynaptic potentials (EPSPs) is dependent on dopamine D1 receptor modulation. (35). The bupropion effects of interaction of dopamine D1 and NMDA receptors, that it may be mediate NMDA complex of glutamatergic synaptic responses and those parameters of synaptic responses such as PS amplitude in the brain regions have not been studied.

Conclusion

There are some mechanisms involved in production of PS which can affect by perinatal exposure of bupropion. Perinatal bupropion exposure affected the dose dependant mechanism(s) involved in the adaptation of the synaptic efficiency. Other studies about synaptic effects of antidepressants postulated that some neurotransmitters such as dopamine, GABA and glutamate can mediate bupropion synaptic effects.

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References

1. Hayford KE, Patten CA, Rummans TA, Schroeder DR, Offord KP, Croghan IT, *et al*. Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. Br J Psychiatry 1999; 174:173-178.
2. Balfour DJ. The pharmacology underlying pharmacotherapy for tobacco dependence: a focus on bupropion. Int J Clin Pract 2001; 55:53–57.
3. Ascher JA, Cole JO, Colin JN, Feighner JP, Ferris RM, Fibiger HC, *et al*. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995; 56:395-401.
4. Dwoskin LP, Rauhut AS, King- Pospisil KA, Bardo MT. Review of the pharmacology and clinical profile of Bupropion, an antidepressant and tobacco use cessation agent. CNS Drug Rev 2006; 12:178-207.
5. Ferris RM, Beaman OJ. Bupropion: a new antidepressant drug, the mechanism of action of which is not associated with down-regulation of postsynaptic beta-adrenergic, serotonergic (5-HT2), alpha 2-adrenergic, imipramine and dopaminergic receptors in brain. Neuropharmacology 1983; 22:1257-1267.

6. Dong J, Blier P. Modification of norepinephrine and serotonin, but not dopamine, neuron firing by sustained bupropion treatment. Psychopharmacology 2001; 155:52-57.
7. ElMansari M, Ghanbari R, Janssen S, Blier P. Sustained administration of bupropion alters the neuronal activity of serotonin, norepinephrine but not dopamine neurons in the rat brain. Neuropharmacolology 2008; 55:1191-1198.
8. Li SX, Perry KW, Wong DT. Influence of fluoxetine on the ability of bupropion to modulate extracellular dopamine and norepinephrine concentrations in three mesocorticolimbic areas of rats. Neuropharmacology 2002; 42:181–190.
9. Mansvelder HD, Fagen ZM, Chang B, Mitchum R, Mc Gehee DS. Bupropion inhibits the cellular effects of nicotine in the ventral tegmental area. Biochem Pharmacol 2007; 74:1283-1291.
10. Placzek AN, Zhang TA, Dani JA. Nicotinic mechanisms influencing synaptic plasticity in the hippocampus. Acta Pharmacol Sin 2009; 30:752–760.
11. Kauer JA. Learning mechanisms in addiction: synaptic plasticity in the ventral tegmental area as a result of exposure to drugs of abuse. Annu Rev Physiol 2004; 66:447-475.
12. Garrett BE, Rose CA, Henningfield JE. Tobacco addiction and pharmacological interventions. Expert Opin Pharmacolther 2001; 2:1545-1555.
13. Dani JA, De Biasi M. Synaptic plasticity and nicotine addiction. Neuron 2001; 31:349-352.
14. Jones S, Bonci A. Synaptic plasticity and drug addiction. Curr Opin Pharmacol 2005; 5:20-25.
15. Gould TJ. Nicotine and hippocampus- dependent learning. Mol Neurobiol 2006; 34:93–107.
16. Kenney JW, Gould TJ. Modulation of hippocampus-dependent learning and synaptic plasticity by nicotine. Mol Neurobiol 2008; 38:101- 121.
17. Watanabe Y, Saito H, Abe K. Tricyclic antidepressants block NMDA receptor-mediated synaptic responses and induction of long term potentiation in rat hippocampal slices. Neuropharmacology 1993; 32:479– 486.
18. Stewart CA, Reid IC. Repeated ECS and fluoxetine administration have equivalent effects on hippocampal synaptic plasticity. Psychopharmacology 2000; 148:217–223.
19. Birnstiel S, Haas HL. Acute effects of antidepressant drugs on long-term potentiation (LTP) in rat Hippocampal slices. Naunyn-Schmiedebergs Arch Pharmacol 1991; 344:79-83.
20. Crawley JN, Gerfen CR, Rogawski MA, Sibley DR, Skolnick P, Wray S. Synaptic plasticity in the hippocampal slice preparation. In: Taylor GP. editors. Current protocols in neurosci John Wiley & Sons, Inc.; 2003.
21. Wang T, Kass IS. Preparation of brain slices. In: Rayne RC. editor. Methods in molecular biology Totowa: Humana Press Inc; 1997.p.1-14.
22. Massicotte G, Bernard J,Ohayon M. Chronic effects of trimipramine, an antidepressant, on hippocampal synaptic plasticity. Behav Neural Biol 1993; 59:100-106.
23. Langosch JM, Walden J. Affects of the atypical antidepressant trimipramine on neuronal excitability and long-term potentiation in guinea pig hippocampal slices. Progress in Neuro- Psychopharmacol Biological Psychia 2002; 26:299-302.
24. Stewart CA, Reid IC. Antidepressant mechanisms: functional and molecular correlates of excitatory amino acid neurotransmission. Mol Psychiatry 2002; 7:15–22.
25. D'Sa C, Duman RS. Antidepressants and neuroplasticity. Bipolar Disord 2002; 4:183–194.
26. Duman RS, Malberg J, Thome J**.** Neural plasticity to stress and antidepressant treatment. Biol Psychiatry 1999; 46:1181-1191.
27. Castren E. Neurotrophic effects of antidepressant drugs. Curr Opin Pharmacol 2004; 4:58-64.
28. Zahorodna A, Bijak M. An antidepressant induced decrease in the responsiveness of Hippocampal neurons to group I metabotropic glutamate receptor activation. Eur J Pharmacol 1999; 386:173–179.
29. Yashiro K, Philpot BD. Regulation of NMDA receptor subunit expression and its implications for LTD, LTP, and metaplasticity. Neuropharmacology 2008; 55:1081-1094.
30. Bobula B, Tokarski K, Hess G. Repeated administration of antidepressants decreases field potentials in rat frontal cortex. Neuroscience 2003; 120:765–769.
31. Popoli M, Gennarelli M, Racagni G. Modulation of synaptic plasticity by stress and antidepressants. Bipolar Disord 2002; 4: 166-182.
32. Reid IC, Stewart CA. Brain plasticity and antidepressant treatments: new cells, new connections. Neurotox Res 2004; 6:483-491.
33. Mc Bain CJ, Freund TF, Mody I. Glutamatergic synapses on to Hippocampal interneuron: precision timing without lasting plasticity. Trends Neurosci 1999; 22:228-235.
34. Baskys A, Wang S, Remington G, Wotjtowicz JM. Haloperidol and loxapine but not clozapine increase synaptic responses in the hippocampus. Eur J Pharmacol 1993; 235:305–307.
35. Chen Long, Charles R Yang. Interaction of dopamine D1 and NMDA receptors mediates acute clozapine potentiation of glutamate EPSPs in rat prefrontal cortex. J Neurophysiol 2002; 87:2324–2336.