Executive Summary of the Project entitled

Modulatory effect of ethanol on olanzapine treated methylphenidate induced mania and corticosterone induced depression in Swiss albino mice

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Principal Investigator

Dr. E. Balamurugan
Assistant Professor
Department of Biochemistry and Biotechnology
Faculty of Science
Annamalai University
Annamalainagar- 608 002
TamilNadu

SUMMARY OF THE FINDINGS

Healthy and peaceful living is a goal for each and every human across the globe. Increased modernization have led to a stressful life thus it leads to a change in mood, behavior, life style, food habits etc. These changes give path to bipolar disorder (BD), which is characterized by mania and depression. BD is connected to change in behavior/mood as it occurs predominantly in the brain cells its complications extends to all parts of the body and leads to changes in neurotransmitter level, hormonal secretion, genetic modification and so on. People affected by BD fragmentally consume alcohol is an notable change in their life style. Hence this present study was focused to evaluate the changes occurs when EtOH consumed during the treatment (with modern drug) of mania and depression in an experimental model.

Several modern drugs are employed in the treatment of BD. One among such universally accepted drug is olanzapine (OLZ), it controls both mania and depression. MPD induced mania and CORT induced depression are frequently used animal models to find out the changes occur in BD. Thus in this study MPD and CORT was used as an inducer for mania and depression in male Swiss albino mice and OLZ as an standard reference drug.

Behavior analysis of the rodents confirms the effect and the role of the inducers. Open field test, Forced swim test, IR actimeter test, Tail suspension test and Rotarod test were considered to analyze the changes in the behavior of control, manic and depressive mice.

Neurotransmitter changes occur in each group of experimental design was relied on the level of dopamine (DA), norepinepherine (NE), serotonin (5HT) and γ-aminobutyric acid (GABA). The levels of hormone play a vital role in the normal body functions. Hormones such as T3, T4, TSH, Testosterone, Prolactin, Cortisol, ACTH, Insulin and C-Peptide were assessed on control, manic and depressive mice. Histopathological examination was carried out in brain PFC and corpus cavernosum. The gene expression (GSK-3β, Akt, β-catenin and WNT) analysis was employed to view, change in brain PFC by using RT-PCR. Upon continuous administration of MPD and CORT, on 10th day MPD administrated mice reflects manic like behavior and CORT administrated mice exhibits depressive like behavior on 15th day in above said behavioral study. Treatment protocol was continued for 21 days as described in experimental period.

MPD administrated group indicated significantly increased locomotor activity observed in central, peripheral and rearing as compared to the control group. Administration of MPD with OLZ significantly showed decreased in locomotor activities when compared to MPD

administrated group. The co-administration of OLZ with EtOH on MPD and MPD with EtOH showed enhanced activity of these locomotor activities when compared to the MPD alone group. CORT administrated group indicates significantly decreased locomotor activity as compared to the mice of the control group. Administration of CORT with OLZ significantly showed improvement in locomotor activities when compared to CORT administrated group. The co-administrated of OLZ with EtOH on CORT and CORT with EtOH showed enhanced locomotor activity of these behaviors when compared to the CORT alone group.

MPD administrated mice significantly increased swimming and decreased immobility time when compared with the control group. MPD treated with OLZ significantly decreased swimming time and increased immobility time when compared with MPD alone group. Reduced swimming time and enhanced immobility time were observed in EtOH alone and combined OLZ with EtOH treated groups of MPD administered mice when compared to MPD alone treated group. CORT administrated mice significantly decreased swimming and increased immobility time when compared with the control group. Reduced swimming time and enhanced immobility time were observed in EtOH alone and combined OLZ with EtOH treated groups of CORT administered mice when compared to CORT alone treated group. CORT treated with OLZ significantly increased swimming time and decreased immobility time when compared with CORT group.

MPD administrated group showed significantly increased hyperactivity fast movement (FM), fast stereotypic movement (FS), and decreased hypoactivity slow movement (SM) and slow stereotypic movement (SS) activities when compared to the control group. MPD with OLZ treatment led to a significantly improved hyperactivity FM, FS and hypoactivity SM, and SS when compared to CORT treated group. MPD treated EtOH and CORT treated combined EtOH with OLZ were significantly increased hyperactivity (FM and FS), and hypo activitiy (SM and SS) when compared to the MPD alone administrated group. CORT administrated group showed significantly decreased hyperactivity FM, FS and increased hypoactivity SM and SS activities as compared to the control group and these loco motor activities were observed using IR actimeter. CORT with OLZ treatment led to a significantly improved hyperactivity FM, FS and hypoactivity SM, and SS when compared to CORT alone treated group. CORT treated EtOH alone and CORT treated combined EtOH with OLZ were significantly increased hyperactivity

(FM and FS), and hypo activitiy (SM and SS) in IR actimeter when compared to the CORT administrated group.

MPD administrated group shows significantly decreased immobility when compared to the control group. MPD with OLZ significantly increased the immobility time when compared to the MPD group. Whereas, MPD treated EtOH and MPD treated combined EtOH with OLZ significantly increased the immobility state when compared to the MPD administrated group. CORT administrated group shows significantly increased immobility when compared to the control group. CORT with OLZ significantly decreased the immobility time when compared to the CORT group. CORT treated EtOH and CORT treated combined EtOH with OLZ significantly increased the immobility state when compared to the CORT administrated group.
MPD administrated group shows significantly increased rotarod performance when compared to the control group. MPD with OLZ significantly decreased the rotarod performance when compared to the MPD group. Whereas, MPD treated EtOH and MPD treated combined EtOH with OLZ significantly increased the rotarod performance when compared to the MPD administrated group. CORT administrated group shows significantly decreased rotarod performance when compared to the control group. CORT with OLZ significantly increased the rotarod performance when compared to the CORT group. CORT treated EtOH and CORT treated combined EtOH with OLZ significantly decreased the rotarod performance when compared to the CORT administrated group.

MPD administrated mice increased DA, NE and 5-HT levels when compared with the control group. In addition, MPD treated mice significantly decreased GABA level when compared with the control group. Our result reports that OLZ treated MPD mice considerably, decreased DA, NE, 5-HT and increased GABA levels when compared to MPD alone. MPD with EtOH and MPD treated combined OLZ with EtOH treated mice also enhanced the DA, NE, GABA and decreased 5-HT levels when compared to MPD treated group. The results were depicted (Table 1). No significant differences were found in control and control accompanied by OLZ treated group in all the behavioral and neurotransmitter levels. CORT administrated mice decreased DA, NE, 5-HT and GABA levels when compared with the control group. Our result reports that OLZ treated CORT mice considerably, increased DA, NE, 5-HT and GABA levels when compared to CORT. CORT with EtOH and combined OLZ with EtOH treated mice also

enhanced the DA, NE, 5-HT and GABA levels in CORT administered mice when compared to CORT treated group.

MPD administered mice decreased levels of T3, T4, TSH, testosterone, prolactin, insulin C-peptide and increased cortisol, ACTH levels when compared to the control group. MPD treated with OLZ increased the levels of T3, T4, TSH, testosterone, prolactin, insulin, C-peptide and decreased cortisol, ACTH in comparison to the MPD group. MPD treated EtOH and MPD treated combined EtOH with OLZ significantly decreased the levels of T3, T4, TSH, testosterone, insulin, C-peptide and increased prolactin, cortisol, ACTH when compared to the MPD alone administrated group. CORT administration decreased levels of T3, T4, TSH, testosterone, prolactin and increased cortisol, ACTH, insulin and C-peptide levels when compared to the control group. CORT treated with OLZ increased the levels of T3, T4, TSH, testosterone, prolactin, insulin, C-peptide and decreased cortisol, ACTH in comparison to the CORT group. CORT treated EtOH and CORT treated combined EtOH with OLZ significantly decreased the levels of T3, T4, TSH, testosterone, insulin, C-peptide and increased prolactin, cortisol, ACTH when compared to the CORT administrated group.

MPD induced manic and CORT induced depressive mice showed that no more significant found in GSK-3β, Akt, β-catenin and WNT expression in PFC when compared with the control groups. Whereas, OLZ treated mice significantly reduced the expressions of GSK-3β, β-catenin and WNT in both manic and depressive mice and no more significant found in Akt expression. In addition, EtOH treated alone and combined OLZ with EtOH mice showed significantly enhanced levels in the GSK-3β, Akt and no more significant changes found in β-catenin and WNT expression in both manic and depressive mice.

From these results it is evident that, the EtOH have impaired the OLZ treatment in both manic and depressive mice. Further it worsens the manic and depressive condition of the mice treated with OLZ. Thus present study concludes that EtOH intake during mania and depression treatment further enhances the diseased conditions.