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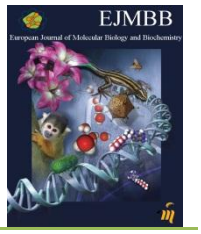

EFFECTS OF LITHIUM AND CAFFEINE ON METHYLPHENIDATE INDUCED ENDOCRINOLOGICAL ALTERATION IN AN ANIMAL MODEL OF MANIA

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ABSTRACT

This is the first study to examine the endocrinological role of caffeine (CAF) in lithium chloride (LiCl) treated methylphenidate (MPH) induced mania in mice. Previous evidence suggests that a hypothalamo-pituitary-thyroid (HPT) axis dysfunction and testosterone level is related to the pathophysiology and clinical course of bipolar mania. The prevalence of thyroid dysfunction is also likely to be greater among patients with rapid cycling and other refractory forms of the Bipolar disorder (BPD). Our results indicated that MPH treatment decreased the T3 and T4 levels, whereas TSH levels have been increased in mice serum. Testosterone levels were increased in MPH treated mice and it has been reverted by the combined LiCl and CAF treatment. The levels of thyroid hormone were normalized by the synergistic effects by CAF with LiCl. This study suggests that testosterone levels may be related to the course of bipolar disorder and suicidal behavior. Further studies of the role of CAF with LiCl co-administration in the neurobiology of bipolar mania are merited.

INTRODUCTION

Bipolar mood disorder (BPD) is a neuropsychiatric disorder leading to unusual shifts in a person's mood, energy, and ability to execute normal daily functions. The major diagnostic clinical feature is the manic episodes characterized by an elated or irritable mood, reduced need for sleep, psychomotor activation, and excessive involvement in potentially problematic behavior [1]. Disorders of the thyroid gland are frequently associated with severe mental disturbances [2,3]. The endocrine system is responsible for physiological integration of multiple organs by different actions of the endocrine axis. However, hormonal effects are not only determined by circulating levels, but also by the time that the organ is exposed to a specific hormone. For example, an acute rise in cortisol concentration is associated with increased attention [4] but raised concentrations, sustained chronically, reduce synaptic and neuronal populations in the hippocampus [5]. Thyroid hormones have a profound influence on behavior and mood, and appear to be capable of modulating the phenotypic expression of major affective illness [6, 7, 8, 9]. Thyroid supplementation is now widely accepted as an effective treatment option for patients with affective disorders [10, 11, 12]. Testosterone plays a major role in a number of physiological processes. Alterations in plasma testosterone concentration and the hypothalamic-pituitary-gonadal axis (HPG) are also associated with psychiatric disorders including mood disorders, psychosis and aggression [13,14]. The association between thyroid functions and behavioural disturbances has been known for the last several hundred years. Although the effects of thyroid hormones on the developing brain were recognized long ago, recent advances in biotechnology have led to an improved understanding of the impact of thyroid functions on the adult, mature brain [15]. Testosterone plays a major role in a number of physiological processes. Alterations in

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plasma testosterone concentration and the hypothalamic-pituitary-gonadal axis (HPG) are also associated with psychiatric disorders including mood disorders, psychosis and aggression [13,14,16,17,18]. Testosterone has also been described as a biomarker for social and economic interactions as well as for status seeking behavior [19]. However, testosterone and other androgens might be involved in the pathophysiology of mood disorders and suicidal behavior. The data on the relationship of testosterone to suicidal behavior have been less consistent. Some studies reported low plasma testosterone levels after suicide attempts [20, 21]. A recent study reported that there was no difference in testosterone levels between male suicide attempters and healthy controls [22]. However, the neuropharmacological effects and functional pathways underlying the therapeutic effects of thyroid hormones in patients with affective disorders are still unclear. Caffeine is probably the most commonly consumed neutrally active compound, but its neuroendocrine effects have not been studied in combination with mood stabilizers. Our previous study reports the combined lithium and caffeine exert antioxidant like properties in the brain of mice induced by MPH [23]. The present study aimed to elucidate the influences of caffeine and lithium in methylphenidate induced mania in mice.

MATERIALS & METHODS

Drugs and Chemicals

Methylphenidate hydrochloride (MPH, Ritalin, Novartis Pharmaceutical Inc.), Lithium chloride (LiCl), Caffeine (CAF) was purchased from Sigma-Aldrich (USA). Electrochemiluminescence immunoassay kits were purchased from COBAS (Elecsys; Roche; cat. no. 11731360, 12017709, 11731459 and 05200067).

Animals

Male *Swiss albino mice* (weighing 25-30g) will be housed in well ventilated rooms (temperature 23 ± 2°C, humidity 65-70% and 10 h light/dark cycle) at Central Animal House, Department of Experimental Medicine, Rajah Muthiah Medical College, Annamalai University and feed with standard pellet diet and water *ad libitum*. All studies will be carried out in accordance with Indian national law of animal care and use, and committee for the purpose of control and supervision of animals of Rajah Muthiah Medical College and hospital (Reg No./160/1999/CPCSEA), Annamalai University, Annamalainagar.

Model of MPH-induced Mania and Experimental Protocol

Methylphenidate (MPH) was suspended in two drops of Tween 80 and saline and administered subcutaneously (sc) at a dose of 5.0 mg/kg b w for 14 days [24]. Lithium chloride (LiCl) was administered intraperitoneally at a dose of 47.5 mg/kg b.w [25] and caffeine 10 mg/kg b.w [26]. All injections were given 20 min before behavioral testing at a volume of 5-ml/kg body weight. In our experiment, a total of forty eight mice were used. The mice were divided into eight groups of six mice each. Group I: Control (saline 2mg/kg/b.w); Group II: Control + LiCl; Group III: Control + CAF; Group IV: LiCl + CAF; Group V: Mania (MPH alone); Group VI: Mania + LiCl; Group VII: Mania + CAF; Group VIII: Mania+ LiCl + CAF. LiCl and CAF will be administered for after the significant increase in the locomotors activity, which will be monitored from the 3rd day onwards.

Blood Sampling and Hormone Analyses

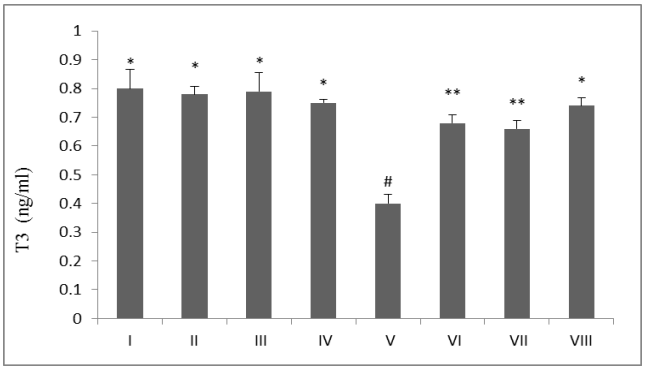
All experimental mice were sacrificed immediately after the last morning application of drug treatment at the same time by decapitation between 9:00 and 11:00 h with a minimum of disturbance in an adjacent room. Blood samples were collected and centrifuged at 1575g for 10 min and frozen at -20ºC until assayed for hormone levels. All samples for hormone measurement were always quantified in the same assay and the intra-assay coefficients are given in parenthesis. Plasma levels of T3, T4, TSH and testosterone were measured by electrochemiluminescence immunoassay (Elecsys; Roche; cat. no. 11731360, 12017709, 11731459 and 05200067, respectively) on a Cobas e 411 analyser (Roche). Measurements were done following the kit procedure.

STATISTICAL ANALYSIS

All the values were expressed as mean ± S.D. of six determinations. Statistical analyses of the data were carried out by one-way ANOVA on SPSS (Statistical package for social sciences) and the group mean compared by Duncan's Multiple Range Test (DMRT). The results were combined as one data set because no significant differences were observed between the control groups. In all comparisons, statistical significance was set at $p < 0.05$.

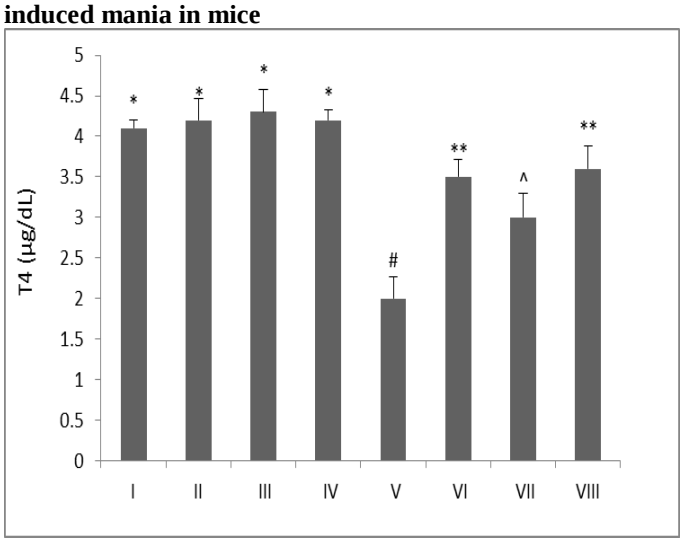
RESULTS

Figure 1. Effect of LiCl and CAF on serum T3 in MPH induced mania in mice



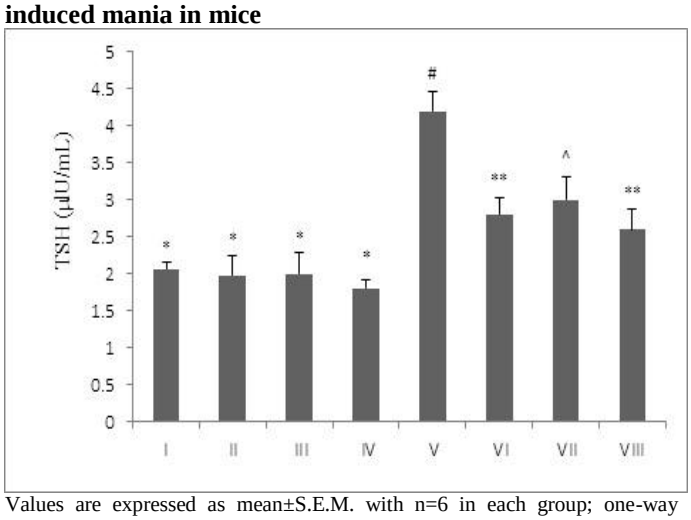
Values are expressed as mean±S.E.M. with n=6 in each group; one-way ANOVA followed by Duncan's Multiple Range Test (DMRT). Values not sharing a common marking (*, **, #, etc.) differ significantly at P<0.05 (DMRT). Statistical evaluation of the data revealed a difference among groups. The MPH administration reduced the levels of T3 & T4. LiCl alone and combined LiCl+CAF significantly (*P*<0.05) increased the T3 and T4 levels when compared to the control groups, whereas CAF alone treatment showed the minor alteration (Figure 1 & Figure 2).

Figure 2. Effect of LiCl and CAF on serum T4 in MPH induced mania in mice



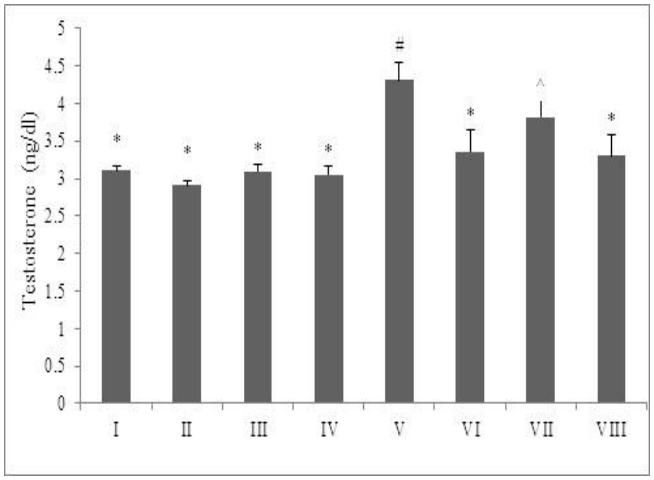
Values are expressed as mean±S.E.M. with n=6 in each group; one-way ANOVA followed by Duncan's Multiple Range Test (DMRT). Values not sharing a common marking (*, **, #, etc.) differ significantly at P<0.05 (DMRT). The increased levels of TSH in MPH treated group were observed, after treatment with LiCl+CAF significantly (*P*<0.05) decreased the TSH levels (Figure 3), while LiCl alone and CAF alone also slightly modifies the TSH levels.

Figure 3. Effect of LiCl and CAF on serum TSH in MPH induced mania in mice



Values are expressed as mean±S.E.M. with n=6 in each group; one-way ANOVA followed by Duncan's Multiple Range Test (DMRT). Values not sharing a common marking (*, **, #, etc.) differ significantly at P<0.05 (DMRT). The testosterone values were shown in Figure 4. Testosterone concentrations between control and treatment groups revealed significant (*P*<0.05) difference among groups. The levels of testosterone were increased in MPH treated groups, combined LiCl+CAF and LiCl alone significantly (*P*<0.05) reversed the levels, while CAF alone did not show any significant effect.

Figure 4. Effect of LiCl and CAF on serum testosterone in MPH induced mania in mice



Values are expressed as mean±S.E.M. with n=6 in each group; one-way ANOVA followed by Duncan's Multiple Range Test (DMRT). Values not sharing a common marking (*, **, #, etc.) differ significantly at P<0.05 (DMRT)

DISCUSSION

The association between thyroid functions and behavioral disturbances has been known for the last several hundred years. This paper attempts to explore the links between thyroid hormone physiology and the presentation and pathogenesis of bipolar disorder. Only a few instances of mania or hypomania associated with hypothyroidism have been reported in the literature [27]. Underlying mechanisms are less clear; they could include dysregulation of CNS catecholamine receptor sensitivity, associated thyroditis and thyrotoxicosis, or a disruption of circadian rhythms [28]. LiCl and CAF modulates the T3 and T4 levels inhibited by MPH induce mania mice. The antithyroidal effect of LiCl were well documented [29,30]. Lithium is concentrated by the thyroid gland and inhibits thyroidal iodine uptake, alters thyroglobulin structure, inhibits thyroid hormone secretion, and interferes with the deiodination of T4 to T3 by inhibiting type-II deiodinase in the brain [31]. The levels of TSH increased by MPH have been decreased by the combined LiCl and CAF administration. Previous reports support our finding that Lithium may evoke an exaggerated TSH response to TRH [32]. Additionally, lithium alters cellular responsiveness to thyroxine, and influences thyroid hormone receptor gene expression [33]. LiCl and CAF reduced the increased levels of Testosterone induced by the administration of MPH. In contrast, lithium has been proven to reduce the circulating testosterone levels in mice [34]. Caffeine, a phosphodiesterase inhibitor, has a stimulatory effect on intracellular cAMP production, which functions as a second messenger and mediates all the intercellular effects of TSH [35,36].

In conclusion, our results suggest that daily CAF intake may exert beneficial synergistic effects with LiCl on the development of thyroid proliferative lesions in mice, partly through a hypothalamus-pituitary-thyroid axis pathway. This could be important in the safety assessment of caffeine consumption in mood disorders. Further studies are required for the mechanisms underlying co-promoting effects of caffeine intake during lithium treatment in mania.

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