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Behavioral, Biochemical and Hematological Studies of New Synthetic Adrenergic Related Antidepressant Compound on Rats

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Abstract

The present study concerns behavioral, biochemical and hematological effects of new synthesized adrenergic related compound 1-(3, 4-dihydroxyphenyl)-2-(4-methylpiperidin-1-yl) ethan-1-one, which have similar structural activity to adrenergic receptor agonist. With intraperitoneal injection in rats, stimulatory activity in home cage, anxiolytic effect in light and dark and locomotors activity in open field were significantly increased. Biochemical effects of glucose and cholesterol were checked by kit (CHOD-PAP) method were significantly decreased. Liver enzymes including, Alkaline Phosphatase (ALP) and SGOT were markedly decreased but, Alanine aminotransferase (ALT) level was markedly increased. In hematological study, after administration of compound hemoglobin (Hb) level was significantly increased in test group of rats. Results indicate that new adrenergic related antidepressant compound not only enhanced the stimulation, locomotion and released depression and anxiety but also, this antidepressant compound show more effectiveness in depression to prevent diabetes and heart diseases.

Keywords: Adrenergic compound; Piperidine; Antidepressant; Blood glucose

Introduction

Newer classes of antidepressants are better tolerated and associated with fewer drug interactions than the older class of antidepressants. Side effects and drug interactions are barriers to successful treatment [1]. Adrenergic related compounds are the chemical compounds which perform their pharmacological and therapeutic effects by increasing or decreasing the activity of various components of sympathetic division of the autonomic nervous system [2,3]. It produces effects similar to stimulation of sympathetic nervous activity is known as sympathomimetic or adrenergic stimulant [4,5]. Adrenergic α receptor leads to the postsynaptic and are widely distributed in CNS and peripheral tissues [6]. It has several functions as vasoconstriction of vein, inhibition of insulin and induction of glucagon from pancreas. β receptors belong to G protein coupled receptors, increase renin and ghrelin secretion, stimulates insulin secretion from pancreas, increase cardiac output by increasing heart rate etc [7,8]. Alanine aminotransferase present in liver and kidney used to screen for monitoring of liver disease, viral hepatitis and tumor necrosis. Alkaline phosphatase is a hydrolase enzyme used to evaluate the liver and bones diseases [9]. High level of ALP includes; leukemia, lymphoma, osteomalacia, bone condition, Paget's disease and hepatitis. It was previously studied that serum glutamic oxaloacetic transaminase (SGOT) is used as a biochemical marker for the diagnosis of acute myocardial infraction. SGOT used for such diagnosis is reductant now and has been superseded by the cardiac troponins [10]. "The role of existing and novel cardiac biomarkers for cardio protection" is current opinion in investigational drugs [11]. Increase level of SGOT also related to gallbladder disease, liver infection, drug abuse, toxin (such as alcohol), pancreas inflammation, kidney injury, dermatomyositis (muscles disease), hemolysis and cancer. So, the aim of the present study is to introduce the newly synthesized compound which is very closely related to EP and NE structurally and the functions are also similar but the advantage of this compound is that it not only decreases the blood glucose level but also improves other hematological and biochemical parameters.

Material and Methods

Synthesis of compound

4-methyl piperidine and 2-chloro 3, 4 hydroxy acetophenone were dissolved separately in 15-20 ml of acetone and then mixed. Reaction mixture was stirred for 60 hours at low temperature at 50-53°C, process of reaction was monitored through thin layer chromatography and the crude solid product was filtered and washed with acetone. The product thus obtained was purified through recrystallization by using methanol and ethyl acetate. The purified compound was dried in desiccators over anhydrous Calcium sulfate.

Preparation of injection for rats

Synthetic compound was dissolved in methanol/ethanol. But, compound was not completely soluble in methanol/ethanol. So slightly warm. Rats were injected intraperitoneally with 98% compound, saline and parent compound. For the preparation of saline 4.5 gm Nacl was dissolved in 500 ml water and then, it was freezed to get chilled saline.

Experimental protocol

Bred male albino Wister rats, weighting 180-200 gm purchase from animal house, research institute of Agha Khan University Karachi Pakistan. Ethical approval was obtained from ethical review board of Federal Urdu University of Arts Science and Technology. Individually all rats were housed in specially designed cages with saw dust covered floor in a quiet room, with free access to cubes of rats' water and food for at least 3 days before treatment, so that the rats could adapted the new environment. The room temperature was maintained between

24°C to 25°C. Rats were categorized into 3 groups, control group (CG), test group (TG) and parent group (PG), in each group six rats were included. Rats were injected intraperitoneally 30 mg/kg body weight with saline in CG, synthetic compound in TG and parent compound in PG.

After 1 hour of injection behavioral activity was monitored for 5 minutes in open field, the apparatus consist of box, having square area (76 × 76 cm) with walls of 42 cm high and floor of the apparatus was divided by lines into 25 squares having equal size. After 5 minutes in home cage apparatus which was specially designed made up of Perspex (26 × 26 × 26 cm) floor was soft due to saw dust. For last 5-minutes light and dark activity was monitored, apparatus was made up of two compartments i.e. one compartment is black and other compartment is transparent and small passage was present between two compartment due to which rats could easily move to either compartment. After monitoring these activities, the rats returned to their cages. Rats were decapitated after 21 hours of injection and then blood and liver were collected quickly within 30 seconds of decapitation stored at low temperature (-70°c) until analyzed for hematological and biochemical analysis. Hemoglobin was estimated by Mindary Automatic Hematology analyzer (888 × 722-61 k-jpg). Concentration of cholesterol and glucose were estimated by CHOD PAP method.

Statistical analysis

Results were represented as mean, ± SD (n=6) significant difference by Newman-keuls test p<0.01 level from TG, CG and PG following one-way ANOVA.

Results

Figure 1 (a) Statistical analysis by one way ANOVA (df3, 18) (f=6.738) (p<0.01) show that after administration of synthetic compound in TG, it shows increase in Novel environment behavior as compare to CG and PG.(b) show statistical analysis by one way ANOVA (df3,15) (f=18.004) (p<0.01) with markedly increase activity in TG as compare to CG and PG. (c) Statistical analysis by one-way ANOVA (df3, 15) (f=1.460) (p<0.01). Results indicate that TG rats spend more time in light box as compare to CG and PG. (d) show light and dark activity (time in sec). Statistical analysis by one-way ANOVA (df3, 15) (f=1.384) (p<0.01), show that entries in light portion in TG increases as compare to CG and PG.

Figure 1 (e) Statistical analysis by one Way ANOVA (df3, 15) (f=193.125) (p<0.01) show after the administration of synthetic compound in TG decrease in cholesterol level as compare to CG. (f) Statistical analysis by one Way ANOVA (df3, 15) (f=28.000) (p<0.01) show after the administration of synthetic compound in TG, significantly decrease blood glucose level in treated rats. (g) Statistical analysis by one-way ANOVA (df3, 15) (f=26014.529) (p<0.01) indicate SGOT markedly decreases in TG treated rats. (h) Show effect of compound on alkaline phosphate level. Statistical analysis by one-way ANOVA (df3, 15) (f=3890.567) (p<0.01) show that after the administration of synthetic compound in TG, ALP level decrease in treated rats as compare to CG and PG. (i) Statistical analysis by one Way ANOVA (df3, 15) (f=278.951) (p<0.01) indicate that ALT level is slightly increase in treated rats as compare to CG and PG.

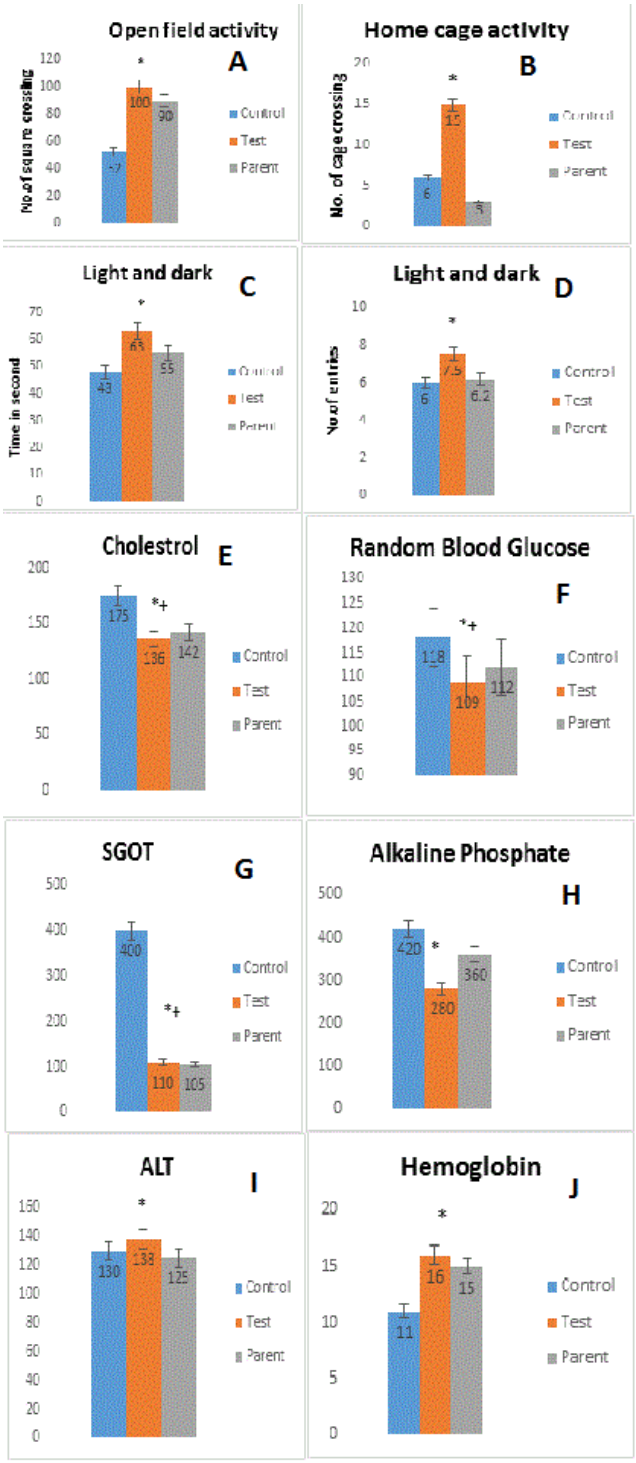

Figure 1: Effect of compound on (a) Open field activity, (b) Home cage activity, (c) Light and dark activity (entries) (d) Light and dark activity (time in sec) (e) Cholesterol (f) Random blood glucose (g) SGOT (h) Alkaline phosphate (i) ALT (j) Hemoglobin respectively. Values are mean, ± SD (n=6) significant difference by Newman-keuls test p< 0.01 level from TG, CG, and PG following one-way ANOVA. *denotes results are significant and *+for more significant.

Discussion

Depression is one of the common psychiatric disease and various antidepressants are prescribed for treatment of depression and other affective disorders, although the molecular and cellular mechanisms by which these agents exert their therapeutic effects are not well understood [12,13]. Previously, it was studied that antidepressant-induced upregulation of neurogenesis would oppose the reduction of hippocampal function and volume that has been reported in patients suffering from depression and other stress-related disorders [14]. Adrenaline is a nonselective agonist of all adrenergic receptors [1]. Previously, people used adrenergic related compound in their life due to pressure full work and sometimes described as getting excess energy from life [15]. Generally, a primary or secondary aliphatic amine separated by 2 carbons from a substituted benzene ring, is minimally required for high agonist activity. It was also studied that if, parent structure for sympathomimetic drugs is substituted by β position of the ethylamine side chain, it not only authorizes the mechanism of sympathomimetic events but also the receptor selectivity of the drug. It was observed that the hydroxyl group on the β carbon, as in norepinephrine and epinephrine, enhances the drug's effectiveness because dopamine which lacks this group is considerably less effective. While the terminal methyl group of epinephrine adds effectiveness, changing this to an isopropyl group drastically reduces activity [16] Present study suggested that after administration of synthetic compound locomotor activity as shown in figure 1(a) increases, stimulatory activity in figure 1(b) also increases and anxiety decreases as shown in figure 1(c) and (d), because time spend and entries in light box increases. Activity takes place normally by adrenergic functioning, but if, its concentration increases or decreases than these activities are affected strongly. High level of SGOT can cause liver damage. AST may be elevated in disease, effecting other organs such as myocardial infraction, acute pancreatitis, sever burn, acute renal disease, musculoskeletal disease and trauma [16,17]. Higher level of ALP is the sign that the bile duct in liver is blocked and not functioning while, ALT also increases with liver damage [18]. Cholesterol is the major indicator of depression. Previous studies show that antidepressant, anticonvulsant and lithium in monotherapy or in combination were associated with decrease in HbA1c levels (19). But, the synthetic compound is called adrenergic compound. Due to phenyl ethyl amine chain, it changes its properties, not only controls the blood sugar level and cholesterol but also significantly increases hemoglobin, liver and cardiac enzymes, indicating good effect of compound.

Conclusion

New adrenergic related antidepressant compound show better activity in the behavioral, biochemical and hematological studies, as activity like stimulatory in self-grooming, standing, relax mood and crossing square in very relax mood were increased. It also releases anxiety and depression in rats. In biochemical tests, it shows decrease in serum cholesterol and blood glucose level in rats. Other test on liver enzymes, shows decrease in ALP, SGOT level and slightly increase in ALT level in rats but do not show any toxic effects. It also increases in Hb level in rats. According to these results, new adrenergic related antidepressant compound, may be used as a good antidepressant in future.

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