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EFFECT OF TRIPHALA ON NOISE STRESS INDUCED ALTERATION IN GLUCOCORTICOID AND CARBOHYDRATE METABOLISM

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ABSTRACT

Stress is a daily phenomenon faced by every living being and it is essential for learning. The body response to stress involves a fight and flight response in which biological changes, prepares the body for emergency action. The aim of the present study is to find out the fifteen days repeated noise, stress exposure induced alterations in the carbohydrate metabolism and its prevention by treatment with Triphala. Wistar strain male albino rats were used for this study. The result shown that the 15 days repeated noise stress (4hrs/day) increases the plasma cortisol level, adrenal body weight ratio, blood glucose, insulin, liver phosphorylase enzyme activity and decreases liver and muscle glycogen stores, the enzyme glycogen synthase activity. These alterations are prevented by treatment with Triphala during stress exposure. These results suggest that Triphala mixture possess the active compounds that have adoptogenic activity and play important role in maintenance of level of the cortisol and carbohydrate metabolism during stress.

KEYWORDS: **Triphala, Noise Stress, Glycogen synthase, Glycogen phosphorylase, Cortisol, Glucose, Insulin.**

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INTRODUCTION

Stress is an everyday event that can have positive and negative effects on the body. Stress can be defined as the non-specific response of the body to any demand made upon it[1] that disturb physiological equilibrium and homeostasis. The stress called eustress makes our body to meet certain challenges while the distress produces harmful effects. Stress, particularly acute stress may improve performance and thus in certain cases be beneficial[2]. However, prolonged or continues stress can be extremely deleterious [3]. When Stress becomes extreme it triggers a wide range of body changes called General Adaptation Syndrome (GAS) which enables an organism to cope with a changing environment. Noise is one of the most widespread sources of environmental stress. Due to the development of industrialization in modern society, noise has become an important stressor that endangers health of humans and welfare of animals[4, 5, 6]. The frequency of the spectrum, magnitude of the sound, duration, aural sensitivity of the listener, and upon the activities being under taken at the time of noise exposure will decide the depth of disturbance caused by noise[7]. Noise exposure result in behavioral suppression, hearing impairment, incidence of birth defect in the offspring and causes time dependent alterations in noise induced plasma catecholamine, ACTH and cortisol concentrations[8]. The studies shown that noise exposure may produce hearing loss, sleep disturbance, hypertension, and ischemic heart diseases[9]. Exposure to low frequency and large amplitude noise resulted in high preponderance of oropharynx infections of viral, bacterial, and fungal origins[10]. The stress hormones such as glucocorticoids, trigger the fight-or-flight response that is intended to save human beings when they are confronted by danger[11]. Stimulation of this system results in increased glucose availability, increased blood flow and increased behavioral responsiveness during stressful situations. Even though the short-term effects of glucocorticoids are essential, the prolonged effects are damaging like immunosuppression (e.g. eosinopenia), insulin resistance (e.g. diabetes), cardiovascular diseases (e.g. hypertension and arteriosclerosis), catabolism (e.g. osteoporosis), intestinal problems (e.g. stress ulcer) [12]. Herbal medicine becomes an integral part of our standard healthcare. There has been a global move in the direction of the use of traditional medicines because of its usefulness and being free from serious toxic effects[13]. Triphala is an Ayurvedic formulation, commonly prescribed by most healthcare practitioners in India[14,15]. It is an equiproportional mixture of fruits of three medicinal herbs, *Terminalia chebula, Terminalia bellirica* and *Emblica officinalis*[14]. It is mild, non-habit forming and rejuvenative, and hence is recommended for all. According to the traditional Indian medicinal system (Ayurveda), Triphala strengthens the different tissues of the body, prevents ageing, and promotes health and immunity [16]. Based on these reports, this study was designed to evaluate the effectiveness of continuous fifteen days treatment of Triphala on the glucocorticoid and carbohydrate metabolism during noise stress exposure.

MATERIALS AND METHODS

Animal species and Chemicals

Wistar strain male albino rats weighing 150-180gm were used for this study. Before the commencement of the experiments, proper permission was obtained from the Institutional Animal Ethics Committee (IAEC no. 8/012/08). Rats were housed under standard laboratory conditions with food and water provided *ad libitum*. All the chemicals used in this study were of analytical grade from SRL and Merck.

Drug and dosage

Fruits belonging to the Triphala formulation were collected from the Chief Botanist, Tamil Nadu Medicinal Plant Farms and Herbal Medicine Corporation (TAMPCOL) Ltd, Chennai, India and authenticated by Director, Centre for Advanced Studies in Botany,

University of Madras. The seedless fruits were dried under shade and powdered before use. Equal proportion (1:1:1) of weighed powder from each fruits (*T. chebula, T. belerica and E. officinalis*) was dissolved in saline (1ml) and administered orally at the dose of 1gm/kg body weight for 15days.

Experimental groups

Twenty four male Wistar albino rats were randomly divided into four groups (Group I, II, III & IV) and each group consists 6 animals. Animals of the Group I were administered with normal saline (1ml) orally for 15 days. Triphala was administrated orally for 15 days in the animals of group II at the dose of 1gm/kg b.wt. Group III animals were subjected to noise stress for 15 days (4hrs/day/100dBA) and also administered with saline (1ml) orally for the same period. Group IV animals were also subjected to noise stress (4hrs/day/100dBA) along with treatment of Triphala (1gm/kg b.wt) for 15 days.

Methodology

Rats were exposed to a broad band (White) noise produced by a white noise generator(graphic-pilot) and amplified by an amplifier (40W) connected to a loudspeaker located at 30 centimeter above the animal cage (3 rats/cage). The intensity of the sound was monitored by a sound level meter (Cygnet systems-D 2023 Serial No.F02199, India) and maintained at 100 dBA intensity[17]. After completion of stress procedure the animals were left in the cages for 24hrs to prevent the overlap of acute stressor effects. On the 16th day animals were sacrificed along with control rats. The blood samples were collected from jugular vein immediately after anaesthetization and were uses for estimation of cortisol, blood glucose level, blood insulin level. Liver and muscle tissue samples were collected for estimation of liver and muscle glycogen content, glycogen synthase, glycogen phosphorylase level. The weight of the animal was taken before and after stress and treatment with Triphala or saline in all the four groups. Weight of the adrenal gland was noted in all the four groups after the killing of the animals. The plasma corticosterone level was estimated by the method of Mattingly[18]. Glucose level in plasma was estimated by using Merck test Glucose kit (GOD POD, NO 11862900011730) from Merck, India, Plasma insulin levels were assayed using standard Mercodia Rat Insulin ELISA enzyme immunoassay kit (no: 10-1124-04) by Mercodia, Sweden. Glycogen was estimated by the method of Hassid and Abraham (1957)[19]. Glycogen synthase, the enzyme was assayed by the method of Leior and Goldenberg (1962)[20]. Glycogen phosphorylase was estimated by method of Comblath et al (1963)[21].

STATISTICAL ANALYSIS

The data are represented in the table as Mean ± SE. The Statistical analysis was done by using SPSS version 10.0 (SPSS, Cary, NC, USA) and one way analysis of variance (ANOVA) with Tukey's multiple comparisons by fixing P value as $p<0.05$ was employed to evaluate the statistical significance between groups.

RESULTS

In all the parameter studied in this study, the Triphala treated control animals remained similar to the control groups. The result shown that a significant increase in the corticosterone level and adrenal body weight ratio in the stressed group animals when compared to the control animals. The pre-treatment with Triphala during noise stress prevents the elevation of corticosterone level and it was similar to control level. The values in the table-1 also indicate the significant increase in blood glucose and insulin level in noise stressed animal when compared to control as well as Triphala treated animal. The animals with Triphala pretreatment during stress markedly decreased the glucose and insulin level from the stressed group and remained similar to control level. A significant decrease in the liver and muscle glycogen level was observed in the stressed animals when compared to the control animals as well as Triphala treated animals. The pretreatment of animals with Triphala

during stress the glycogen content was markedly higher than the stressed animals and moreover these animals showed a similar glycogen level as that of the controls. There was a significant decrease in the level of the enzyme glycogen synthase in the stressed animals compared to the control animals. The pretreatment of animals with Triphala suppressed the decrease of glycogen synthase activity markedly from stressed group animals and level of muscle glycogen was similar to the control.The activity of the another enzyme liver glycogen phosphorylase was significantly increased in stress group The pretreatment of animals with the Triphala before stress prevented the increase in glycogen phosphorylase level and it was similar to the control.

TABLE 1
Effect of Triphala on blood glucose, insulin, cortisol level and carbohydrate metabolizing enzymes

PARAMETERS	CONTROL	TRIPHALA	NOISE STRESS	STRESS+TRIPHALA
Plasma corticosterone (µg / dL of plasma)	44.77 ± 3.69	43.82 ± 2.6	63.02 ± 5.03*	44.74 ± 3.22#
Adrenal body weight ratio (mg/gm bw)	17.34 ± 1.27	17.01± 0.78	26.14 ± 0.9*	16.97 ± 0.98#
Blood glucose (mg/dL of plasma)	110.64 ± 5.96	108.47 ± 6.11	156.44 ± 4.5*	113.42 ± 5.82#
Plasma insulin (pmol)	450.39±24.83	449.82±24.15	654.42±26.56*	452.53±21.98#
Liver glycogen (mg/g of wet tissue)	15.71 ± 1.29	16.31 ± 1.91	9.21 ± 0.91*	15.49 ± 1.19#
Muscle glycogen (mg/g of wet tissue)	4.37 ± 0.38	4.82 ± 0.5	2.21 ± 0.59*	4.29 ± 0.43#
Liver glycogen phosphorylase (micromoles of phosphorus/hr/mg of protein)	638.35 ± 30.84	631.3±27.37	832.6±35.65*	625.43±30.73#
Liver glycogen synthase (micromoles of UDP/hr/mg of protein)	175.84 ± 6.15	171.16±10.9	103.08±8.04*	170.82±10#

Values are in mean ± Standard error; Number of animals in each group = 6;
****p < 0.05 Vs control; #p <0.05 Vs Noise stress.***

DISCUSSION

Former stress physiologists had documented most of the stress induced physiological changes. Many processes intervene between stressful stimulus and subsequent responses in the body. Noise is one of the common and strong environmental stressor for both human and animals. Noise in public places, especially in occupational environment is considered as health hazard[22]. Even though many studies are performed to explain the effect of stress in physiological change only scanty literature evidence exist on effect of noise stress on carbohydrate metabolism. In this study most of the parameters studied revealed that the stress is not yet adapted and there was an increase in the adrenal weight glucocorticoid level and changes in the carbohydrate metabolism even after fifteen days of repeated noise stress. The study conducted by Nirupama et al shown Changes in the activities of key enzymes and substrates of carbohydrate metabolism reveal underlying mechanisms of acute stress-induced elevation in blood glucose level[23]. Metabolic stress responses are mediated by hormones of the adrenal gland [24, 25, 26]. Activation of adrenal glands in stress was due to ACTH, the enhanced level of which always preceded the

elevation of glucocorticoids [27]. This persistent increase in steroid level can be attributed to be due to the changes in the glucocorticoid receptor levels which were associated with the altered glucocorticoid negative feedback sensitivity in rats [28]. ACTH apart from increasing the secretory activity of adrenal cortex could also cause hypertrophy and proliferation of adrenocortical cells [29]. In this study, similar results have been observed in rats subjected to noise, which showed a significant increase in adrenal gland weight ratio Elevation of glucocorticoid causes an increase in glucose production and utilization[30]. The release of catecholamines and subsequently glucagon and corticosterone stimulate glycogenolysis and gluconeogenesis [31]. Acute stress responses could increase the adrenaline, noradrenaline, glucagon and corticosterone levels within minutes [32]. This increase may be to meet certain energy demand in certain body areas. The primary function of cortisol is to promote gluconeogenesis, which is an essential component of our body's adaptation to stress, ensuring that the vital organs have enough energy to meet the increasing workload. This demand triggers mechanisms to compensate for the increased withdrawal of glucose from the blood to tissues. The corticosteroid elevation was accompanied by an increase in blood glucose, insulin and a decrease liver glycogen with the increase in the glycogenolytic enzyme phosphorylase with the decrease in the glycogen synthase's activity[33]. In vitro and in vivo studies also suggest that glucocorticoid excess causes insulin resistance by either altering the binding of insulin to its receptor or impairing the intra-cellular response to insulin[34]. Triphala is one of the oldest and most commonly used polyherbal preparations in the Indian system of medicine. Several studies showed the effect of Triphala on noise stress induced alterations. In this study it shows that pre treatment with Triphala during noise stress significantly decreases the stress induced corticosteroid level, adrenal gland weight, blood glucose level and increased insulin level and changes in the carbohydrate metabolizing enzymes. Triphala has been reported to be a rich source of Vitamin C, ellagic acid, gallic acid, chebulinic acid, bellericanin, β-sitosterol and flavanoids [35]. It also rich in phenols/polyphenols, tannins [36,37] and Mg, K,Ca,Fe,Se, Zinc and gallic acid [38]. The vitamin C, flavonoids, tannins are well known anti-oxidants and it increases the secretion of insulin and decreased the hyperglycemia in diabetic rats due to its anti-oxidants capacity[39].An antioxidant is a molecule stable enough to donate an electron to a rampaging free radical and neutralize it, thus reducing its capacity to damage. The mechanism involves significant inhibition or delay in the oxidative process [40]. The levels of some tissue antioxidants are inversely related to cortisol tissue levels [41]. Antioxidant depletion may result as a consequence of various pathways activated by cortisol or may be the effect of free radical production during cortisol metabolism, that noise-stress significantly increased the lipid peroxidation and corticosterone level with concomitant depletion of antioxidants in plasma and tissues of both non-immunized and immunized rats Further, pre-treatment with Triphala prevented the elevation in the LPO and corticosterone levels associated with noise stress exposure. It indicate that TPL may be a potent and novel therapeutic agent for scavenging of NO, and thereby inhibit the pathological conditions caused by excessive generation of NO and its oxidation product and per oxy nitrite[42]. Since, free radicals have been implicated in the causation of several diseases such as liver cirrhosis, atherosclerosis, cancer, and diabetes; it is obvious that this mixture which could scavenge free radicals have great potential in improving these disease processes[43].The chief ingredients in Terminalia bellirica is ellagic acid and gallic acid, E.officinalis has gallic acid derivatives including epigallocatechin gallate, and T.chebula rich in gallic acid[44]. HPLC analysis showed that Triphala contains 73 ± 5 mg Gallic acid per gram of Triphala [37] and Gallic acid as the major component [45]. Gallic acid increases liver glycogen levels and reduce the serum glucose level [46]. This indicates Gallic acid may produce glucose lowering effects either due to increased sensitivity of peripheral tissue to insulin or direct

insulin-like effects[47]. The above reports indicating that some of the phytochemicals like Gallic acid in the Triphala might be responsible for reducing glucocorticoids that increased by stress and also maintain glucose homeostasis.

CONCLUSION

The present study shown clearly that the Triphala preparation when given orally prevents the noise stress induced alterations in carbohydrate metabolism. This may be due to phytochemical present in the Triphala. It is suggested that further detailed studies are required to find out which phytochemical are responsible for prevention of alteration in carbohydrate metabolism.

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