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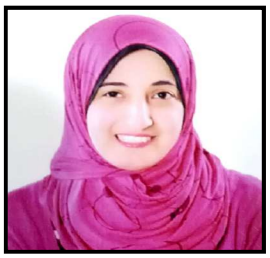

THE VALIDITY OF REGULAR SLEEP TO PREVENT IMPAIRMENT OF PHYSIOLOGICAL ABNORMALITIES IN MICE

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ABSTRACT

This study aims to demonstrate the association between sleep disruptions induced stress in male mice and some physiological functions as well as antioxidant status, where sleep act as restorative process and its deprivations responsible for increasing metabolic disorders. A total 20 adult male mice divided into 2 groups the first 10 act as control, meanwhile, the second 10 exposed daily to sleep deprivation 5 weeks by gentle handling for 6 hrs starting from 7 a.m. Obtained results in sleep deprived group compared to control mice group showed decrease in RBCs, Hb, Ht%, insulin concentration, leptin and melatonin. Also SOD activity decline in concomitant with GSH and plasma iron concentration. But, this group showed significant increase in total leukocytes number, lymphocyte %, ACTH, corticosterone, ghrelin, MDA concentration and CAT activity in association with exceed total lipid and triacyglycerol (TG), IL-2, and IL-6. This study reveal that, sleep loss to mice by gentle handling may act as stressor leads to haematological abnormalities, metabolic disorders, and impair immunity and oxidative status in consequence to stress, physiological, biological, and biochemical mechanisms.

KEYWORDS

Stressor, Sleep deprivation and Antioxidants.

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INTRODUCTON

Sleep is an essential component of animal behavior, controlled by both circadian and homeostatic processes. It is primarily and essentially needed for all vertebrates biologically.

Circadian rhythms are synchronized by environmental cues such as light or feeding. Imbalance of this synchronization is mostly accompanied by sleep circadian rhythms disorders[1].

Sleep abnormalities may lead to metabolic syndrome including dyslipidemia, hypertension, glucose intolerance and central obesity[2].

Females have a higher tendency to metabolic syndrome than males, these syndrome exceed in both sexes with increasing age[3].

Sleep deprivation showed conflicting results about haematological results; Dinges *et al*[4], showed that, sleep deprivation is associated with increased total leukocytes, neutrophils, lymphocyte, and monocyte. But, Boyum *et al*[5], recorded decline in these parameters. In contrast, Ruiz *et al*[6], mentioned that, no effect of sleep deprivation on these parameters, meanwhile, Boudjeltia *et al*[7], showed that, no effect was seen in RBCs in young healthy men after exposure to sleep deprivation.

Fuller *et al*[8], showed that, rodents adjust their sleep onset to match food availability during their sleep-wake cycle. McCoy *et al*[9], noted that, 24h of experimental sleep fragmentation altered rat behavior in an open field. Grooming is an important aspect of the behavioral repertoire in rodents, they are sensitive to stress caused by sleep deprivation[10].

Hairston *et al*[11], showed that, sleep deprivation was accompanied by alterations in glucocorticoid levels in rodents.

Tartar *et al*[12], reported that, plasma corticosterone (CORT) levels significantly elevated in sleep fragmentation or total sleep deprived rats; they determine the role of hypothalamic pituitary adrenal (HPA) axis stress response on some behavior alterations caused by sleep deprivation.

Hormones from the HPA axis like melatonin modulate sleep-wake cycle. In case of its abnormal functions sleep disrupts. Sleep loss influence HPA axis leading to exceed in their activity[13].

Exposure of rats to light decrease 5-hydroxy indol-o-methyl transferase (HIOMT) activity, while their exposure to dark increases its activity under the sympathetic control. The enzyme HIOMT in the pineal gland is important for methylation of N-acetyl serotonin after its conversion from serotonin[14].

Meier *et al*[15], reported that, ghrelin is a peptide secreted by the stomach; stimulate appetite and correlates to hunger. Leptin is essentially secreted from adipocytes, it is decrease to promote caloric storage and exceed to enhance energy expenditure, leptin level decrease by sleep deprivation[16].

Improper sleep is mostly associated with altered the level of hormones related with energy balance such as ghrelin and leptin[17].

Sleep deprivation impairs the viral immune response by exceeding adrenergic signaling of the sympathetic nervous system[18] and lead to a shift away from type 1 T-helper cell immunity[19].

Sleep deprivation may consider psychological stressors which accompanied by decline in the total number of T-cells and reduced mitogen induced lymphocyte proliferation and natural killer cells activity[20].

The present work was undertaking to examine the effect of stress caused by sleep disruption on some physiological changes in male mice.

MATERIAL AND METHODS

Materials

Twenty male Swiss albino mice (Faculty of Medicine breeder, Mansoura University) weighing 24±2g at the commencement of the study were used. They were housed in plastic cages measures 16x16x 10 inches, 5 mice in each cage. They were housing in temperature controlled animal house (23±2^{o}C). Mice had free access to commercial standard chew diet and water.

Ten mice served as control (non sleep deprived), the other ten were suffer from sleep deprived by external stressor using gentle handling through 6h of the day starting from 7.0 a.m., for 5 weeks.

Experimental methods

At the end of experimental period, mice were euthanized and blood was taken via the cardiac puncture in separated EDTA containing tubes.

Tubes were allowed to centrifugation at 800xg for 15 min. plasma were separated and stored at -80^{o}C for further analysis.

Haematological parameters were assessed as described by Dacie and Lewis[21].

Glucose, total lipid, triacylglycerol were estimated according to the methods of Josef[22], Frimgs *et al*[23] and Fossati and Prencipe[24], respectively.

HbA1c in blood was estimated using the ELISA technique: Cat. No. CSB-E08141m.

Insulin, was assessed as recommended by Yallow and Berson[25], where leptin, ghrelin, melatonin, and corticosterone were analyzed: using an enzyme

linked immunosorbent assay (ELSIA kits) (Cusabio, California, USA).

ACTH was analyzed by: electrochemiluminescence assay technique (ECLIA). ROCHE, Germany. Ref (03255751: ACTH) ELISA technique.

Regarding antioxidant markers, Antioxidant enzymes activity SOD and CAT were determined as showed by Nishikimi *et al*[26] and Bock *et al*[27], respectively, where GSH and MDA were assessed by the method of Beutler *et al*[28] and Ohkawa *et al*[29], respectively.

PC level was estimated after Davies and Delsignore[30].

The IL-2 and IL-6% were determined by Using Mouse Interleukin-2 (Cat. No. CSB-E04627m) and Interleukin-6 (Cat. No. CSB-E04639m) ELISA Kits.

The difference between data in both group were examined using student-t-test. A P value less than 0.05 were considered significant. All statistical analyses were conducted using SPSS software[31].

RESULTS AND DISCUSSION

Obtained data in Table No.1 showed that, sleep deprivation significantly decline Ht%, RBCs count, Hb concentration and neutrophils percent in concomitant with exceed leukocyte.

Table No.2 recorded an increase in blood glucose, total lipids, triacylglycerol, ACTH, corticosterone and ghrelin levels. In concomitant with lower leptin level, and hypoinsulinaemia.

Data listed in Table No.3, showed decline in SOD activity, melatonin and GSH levels; this was accompanied by an increase in CAT activity, MDA and PC levels as well as the percentage of interleukins (IL-2 and IL-6) relative to normal central daytime wake-up participants.

Discussion

This study set out to evaluate the interaction between sleep deprivation and metabolic disturbance through haematological, biochemical parameters, oxidative stress markers as well as immune alterations in male mice.

The resulted decline in RBCs, Hb and Ht% in sleep deprived group may be as a result of stress leads to exhaust bone marrow to decrease RBCs synthesis or its fatigue where they fastly destructed[32]. Another putative mechanism for explaining this decline may be due to lower iron content after variation in hepcidin concentration due to circadian rhythm as reported by Kemna *et al*[33], where sleep deprivation significantly reduce the amplitude and reduce iron concentration[34].

Also, haematological markers may alter due to stress that affects body health[35].

Excess in WBCs count in sleep deprived mice group were in agreement with Heredia *et al*[36]. The increased leukocytes count in sleep deprived mice was a sign of host defense activation as reported by[37]. Also, obtained increase in WBCs and some of their subpopulation in sleep deprived group may be an immunosuppresion[38].

The resulted hyperglycemia in association with hypoinsulinamia may be due to metabolic disturbance leading to increase post prandial glucose and cortisol in concomitant with low leptin level[39].

The lower insulin level in sleep deprived group may be attributed to insulin exhaustion of pancreatic sites, as a result of decline insulin resistance at the peripheral receptors sites after sleep deprivation, an explanation which in accordance with Van Helder *et al*[40].

In addition, disturbance in sleep duration and quality may be predictors of glycated haemoglobin (Hb A1c), which is a key marker of glycemic control[41].

The resulted increase in both total lipid and triacylglycerol in sleep deprived group may be attributed to enhancement of ghrelin that signal the brain regarding hunger state of the body[42].

The resulted metabolic syndrome characterized by hyperglycemia and hyperlipidemia in sleep deprived group may be as a result of over expression of 11 β-hydroxy steroid dehydrogenase 1 (11-β-HSD1) as reported by Masuzaki *et al*[43].

In addition, these results may be due to overeating during sleep deprivation, which is a physiological attempt to restore sleep where food intake promopte sleep, an explanation which runs parallel to Penev[44].

The present result showed higher corticosterone level in sleep deprived group, this result in consistent with the opinion Hirotsu *et al*[45], who recorded exceed corticosterone levels in sleep deprived rats which may be due to the stressor

caused by sleep deprivation, which activate glucocorticoid hormone concentration.

Also, Takatsu-Coleman *et al*[46], showed that, sleep deprivation in mice has been extensively acted as stress activated glucocorticoids.

The obtained exceed in ACTH level in sleep deprived mice group are in accordance with Andresen *et al*[47], who clarified that, sleep deprivation in rats is accompanied by higher level of ACTH.

The resulted increase in plasma mice corticosterone level in sleep deprived group was in agreement with Cohen *et al*[48] who noted that, stressor by gentle handling caused sleep deprivation in mice, associated with higher corticosterone level.

It is possible that, loss of normal circadian rhythm in sleep loss caused dysregulation in the normal diurnal variation of corticosterone[12].

The resulted alteration in ghrelin and leptin level in sleep deprived group compared to control group may be due to disrupt in endocrine regulation of energy balance as mentioned by Cummings *et al*[49].

Glutathione peroxidase catalyzes the reduction of the hydroperoxides as H_2O_2 by GSH, and is important to protect the cell from oxidative damage.

The obtained disturbed antioxidant in estimated tested mice influenced by sleep deprivation as mentioned by Ramanathan *et al*[50], who reported that, prolonged (5-11 days) sleep deprivation significantly decreased SOD activity in sleep deprived mice compared to control one.

The recorded exceed in MDA and PC concentrations in sleep deprived group may be related to their expose to stress as sleep deprivation consider as stressor in response to HPA stress[12]. This Stress may lead to oxidation of lipid membrane and carbonylation of protein, an explanation in agreement with Hauck and Bernlohr[51].

The increase in CAT activity in sleep deprived group may be to overcome the excess H_2O_2 resulted from oxidative stress where sleep deprivation may alter the antioxidant activity[50].

The detected depletion in melatonin level in sleep deprived mice may be due to effect of sleep deprivation on the function of brain and many other systems as shown by Tufik *et al*[52].

The elevation in interleukins concentration observed in sleep deprived group may be as a result of fatigue and decline natural killer cells[53].

The obtained disturbance in cytokines may be through the effect of CNS to suppress the trafficking of immune cells from the blood to the tissue, an explanation which coincide with Dhabhar and McEwen[54].

Table No.1: Haematological markers in control and sleep deprived mice groups

S.No	Estimated Parameters / Groups	Hb (g/dl)	RBCs (x 10^6 /mm^3)	Ht %	WBCs (10^3/mm^3)	Lymph. %	Mono. %	Neutro. %	Eosin. %	Baso. %
1	Control	12.8 ± 0.53	7.78 ±0.5	43.5± 1.9	5.52 ± 0.61	57.2 ± 2.09	6.4 ± 0.69	33.5 ± 1.95	1.6 ± 0.51	1.3 ± 0.48
2	Sleep deprived	9.4[a] ± 0.9	5.8[a] ± 0.5	31.9[a]± 3.9	8.93[a] ±0.86	70.8 ± 2.52	9.2 ± 0.63	15.1 ± 3.57	3.3 ± 0.48	1.6 ± 0.51

Table No.2: Some metabolic products and hormonal concentrations in control and sleep deprived mice groups

S.No	Estimated Parameters / Groups	Glucose (mg/dl)	HbA1c (%)	Insulin (ng/ml)	Total lipid (mg/dl)	Triacylglycerole (mg/dl)	ACTH (Pg/ml)	Corticosterone (ng/ml)	Leptin (ng/ml)	Ghrelin (Pg/ml)
1	Control	120.2 ± 1.48	4.66 ± 0.103	0.26 ± 0.06	456.7 ± 5.07	26.7 ± 1.41	0.21 ± 0.008	0.14 ± 0.010	0.33 ± 0.008	0.17 ± 0.008
2	Sleep deprived	132 ± 3.26	5.11 ± 0.301	0.20 ± 0.04	539.8 ± 7.55	44.4 ± 2.41	0.28 ± 0.012	0.19[a] ± 0.004	0.14[a]± 0.007	0.32[a] ± 0.017

Table No.3: Some plasma antioxidant, oxidative stress markers and cytokines in control and sleep deprived mice groups

S.No	Estimated Parameters / Groups	Melatonin (ng/ml)	SOD (U/ml)	CAT (U/l)	GSH (mg/dl)	MDA (nmol/ml)	PC (nmol/ml)	IL-2 %	IL-6 %
1	Control	0.29 ± 0.012	41.03 ± 3.10	188.7 ± 1.76	13.8 ± 0.74	48.82 ± 3.48	0.26 ± 0.01	19 ± 1.69	1.09 ± 0.05
2	Sleep deprived	0.22[a] ± 0.002	20.58[a] ± 1.49	283.4 [a] ± 8.64	4.8 [a] ± 0.47	122.6[a] ± 6.27	0.34 ± 0.01	37.2 [a] ± 1.93	1.53[a] ± 0.08

CONCLUSION

It is concluded that, during normal sleep time, the body heals himself and restores its chemical balance, but sleep deprivation dramatically lower normal physiological functions, disturb metabolism, antioxidants and impairs immunity.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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