

Effect of “Red Bull” Energy Drink on Some Neurotransmitters Content and Histological Structure of Cerebral Cortex in Male Albino Rats

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Abstract: The objective of this study was to investigate the Neurological risks associated with the consumption of energy drink Red bull. The chronic effect of energy drink Red bull on some neurotransmitters contents norepinephrine (NE), dopamine (DA) and gamma-aminobutyric acid (GABA) in different brain regions and histological structure of cerebral cortex of male albino rats. The chronic administration of red bull (3.1 ml/day) caused a significant decrease in neurotransmitter contents in different brain regions and have caused histological changes in the cerebral cortex area led to a atrophy of nuclei nerve cells and abnormalities in pyramidal cells may be due to the effect of caffeine.

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Key words: red bull, neurotransmitter, the cerebral cortex

1. Introduction

Energy drinks are considered in nowadays of the most common food products by different ages, especially young people, believing that It's the recipe that improves their performance and saving energy, often taking Significant amounts in everyday life. There are several reports warning of side effects and even death caused by excessive of energy drinks.

Energy drink is commonly available in grocery stores, bars and super markets and vending machines. These are manufactured in small, bullet-shaped cans (1) for example Power horse, Red bull, Full throttle, Dare devil, Cocaine (2).

Energy drinks have become popular drinks, one of the soft drinks that contain a high concentration of caffeine, methylxanthines, panthenol, vitamin B complex (3), simple sugars (glucose, fructose, galactose and sucrose), carbohydrates, Inositol, maltodextrin, niacin, amino acids: such as (taurine, carnitine and creatine). In addition to a variety of aromatic herbs to give a flavor such as (Guarana, Ginseng, Ginkgo, Biloba, Ephedrine and Yerba Mate), Glucuronolactone metabolite of glucose natural and artificial sweeteners which claims to provide who consume excess energy is due to this term to the manufacturers of liquid drinks, which is not recognized by the Food and Drug Natural Resources USA administration or the US Department of Agriculture (4).

The most common reasons for energy drink consumption include counteracting sleepiness and increasing energy, maintaining alertness while studying and driving (5).

Caffeine is an important substance in energy drinks is responsible for the stimulant effect of the

nervous system (6) and is absorbed from the small intestine and metabolized rapidly in the liver and does not accumulate in the body, but expelled to the outside after several hours of consumption. Caffeine is a diuretic and excessive consumption leads to short-term symptoms, such as a sense of activity and vitality and insomnia and in some cases, lead to side effects on blood circulation and cause depression and hyperactivity (7). Indicate the results of that the effect of caffeine on the white blood cells can lead to worsening of muscle injuries by the exercise (8). Also, it is important to note that the use of caffeine beside exercise leads to activation of the pituitary and adrenal gland, hypothalamus cell and autonomic nervous system (9).

A few amount of caffeine doses (20-200 mg / day) have been effected with positive effects on mood, such as perceived feelings of increased energy, fantasy, efficiency, self-confidence, vigilance, impulse and concentration (10). It was found that intakes of caffeine > 100 mg/day related with elevated blood pressure for adolescents and opposite effects with caffeine consuming in amounts ≥ 400 mg causes nervousness, irritability, insomnia, increased urination, arrhythmia and stomach upset (11). it found that the retreat symptoms of caffeine from the body, causes headache, Irritability, drowsiness, mental confusion, insomnia, tremors, nausea, anxiety, restlessness, increased blood pressure, depression, difficulty concentrating and decline in cognitive performance and found that the same symptoms happen when excess consumption (12).

It found that Taurine in conjunction with caffeine improves concentration and reaction speed while also enhancing emotional status, and use the

Taurine in conjunction with caffeine and glucuronolactone have positive effects on brain function. They also conjectured that Taurine might interact with GABAergic, glycinergic, cholinergic, and adrenergic neurotransmitter systems. Nevertheless, they also agreed upon the possibility that such findings on cognitive performance may have been attributable solely to caffeine. It was found that consumption of taurine alone is not a significant risk to human health (13).

Glucose is thought to improve some aspects of cognitive performance, memory (14). It was found that caffeine and glucose alone and together, reduced reaction time and together improved sustained attention and memory (15).

Studies show that the active ingredients found in most energy drinks (taurine, glucose, caffeine, and many of vitamins B) have a significant effect on the metabolism of the human, energy production, improve cognitive performance and have an important role in cellular functions in the brain (16).

France and some other countries prevented the popular energy drinks, especially Red Bull because they contain excessive amounts of caffeine and Britain issued a warning against Red Bull used by pregnant women and children after the died of Ross Coony athlete because of consuming four cans of Red Bull before the start of play (17).

The aim of this study was to evaluation the effects of Red bull on some neurotransmitters content and the structure of the cerebral cortex region in the brain of male albino rats.

2. Materials and Methods

Chemicals:

Red bull was purchased from local market in Jeddah-Saudi Arabia.

Animals:

This study has been conducted at the King Fahd Medical Research Center in King Abdulaziz University, Jeddah, Saudi Arabia. The experimental animals used in this study a total number of (39) male albino rats and weights between (75 g - 85 g). The rats were housed in plastic cages, each containing 6 animals at a controlled temperature (22 ° C - 25 ° C) 70% relative humidity and air flow conditions with fixed 12 hour light- dark cycles.

Methods:

Experimental Animals:

Rats were randomly divided into three groups. The first group as a control (n = 6) was drink orally a normal water daily by oral tube and then killed at the beginning of the experiment. The second group(n = 24) received orally Red bull (3.1 mg /day) for 3 weeks and then allowed one weeks to recover. Third group(n= 9)received orally Red bull (3.1 mg /day) for

3 weeks and then histological study in cerebral cortex. In the end of experiment were killed rats by sudden decapitation at the designed times. The brain was rapidly excised and then dissected on dry ice glass plate and separated into the following areas: Cerebellum, striatum, cerebral cortex, hypothalamus, brain stem and hippocampus: according to (18). NE and DA were extracted and estimated according to (19) modified by (20). GABA was estimated according to (21). The fluorescence was measured in Jenway 6200 fluorometer.

Histopathological Examinations:(Light Microscopic Study):

Parts of the cerebral cortex were fixed in 10% formalin saline for 72 hoursprepared for histological examination and stained specified in sections haemotoxylin and eosin (H & E). Then slides were examined at magnifications of X40 under light microscope (22).

Statistical Analysis:

The data are presented as mean \pm S.E. Statistical analyses between control and treated animals were performed using paired student 't' (23).

$$\% \text{ difference} = \frac{\text{Treated value} - \text{control value}}{\text{control value}} \times 100$$

3. Results

Physiological results:

The results obtained from **Table (1)**, **figure (1)** showed that the daily oral administration of Red bull (3.1 ml/day) caused no significant in norepinephrine content in the first week and a significant decrease in all of tested areas after second and third week. The maximal decrease ($p < 0.05$) in dopamine content was found in the cerebellum after second week (-23.12%) and striatum after third week (-53.06%). the effect of the withdrawal of the energy drink Red bull sequence of the body on the content of norepinephrine, where results indicate a continued affected in all the studied areas until the end of the withdrawal period.

As shown **Table (2)**, **figure (2)** the daily oral administration of Red bull (3.1 ml/day) caused a significant decreasing in dopamine content in the brain stem after the first week and in the cerebellum, striatum, cerebral cortex, hypothalamus, brain stem and hippocampus in the second and third week. The maximal decrease ($p < 0.05$) in dopamine content was found in the brain stem after one week (-12.08%) and in the cerebral cortex after third week (-47.10%) The effect of the withdrawal of the energy drink Red bull sequence of the body on the content of dopamine, where results indicate a continued decline in the moral of all the studied areas until the end of the withdrawal period.

Also, **Table (3), figure (3)** showed that the daily oral administration of Red bull (3.1 ml/day) caused a significant decrease in gamm-aminobutyric acid content after the first week in cerebellum, striatum, brain stem and hippocampus. Then a significant decrease in all of tested areas after second week until the end of the treatment period. The maximal decrease in gamm-aminobutyric acid content was found in the

hippocampus after first and second weeks (-50.49 %, -56.55%) and the cerebellum (-66.77%) after the third week of treatment. The effect of the withdrawal of the energy drink Red bull sequence of the body on the content of GABA, where results indicate a continued decline in all the studied areas until the end of the withdrawal period.

Table (1): Effect of chronic oral administration and Subsequent withdrawal of Red bull (3.1 ml/day) on norepinephrine (NE) content in the different brain areas of male albino rat.

Time of decapitation		Cerebellum mean \pm S.E.	Striatum mean \pm S.E.	Cerebral cortex mean \pm S.E.	Hypothalamus mean \pm S.E.	Brain stem mean \pm S.E.	Hippocampus mean \pm S.E.
1 week	C	95.382 \pm 0.845	511.473 \pm 1.803	56.203 \pm 0.225	596.997 \pm 3.242	390.050 \pm 0.831	292.540 \pm 1.536
	T	96.600 \pm 1.423	520.833 \pm 5.482	55.812 \pm 0.038	587.719 \pm 5.548	391.233 \pm 0.735	291.542 \pm 0.717
	%	1.28	1.83	-0.70	-1.55	0.30	-0.34
2 weeks	C	95.382 \pm 0.845	511.473 \pm 1.803	56.203 \pm 0.225	596.997 \pm 3.242	390.050 \pm 0.831	292.540 \pm 1.536
	T	73.333 \pm 0.919	456.000 \pm 0.365	45.667 \pm 1.116	588.727 \pm 4.206	335.667 \pm 1.476	289.952 \pm 0.820
	%	-23.12 *	-10.85 *	-18.75 *	-1.39	-13.94 *	-0.88
3 weeks	C	98.688 \pm 0.274	495.653 \pm 1.445	55.493 \pm 0.105	604.906 \pm 2.337	394.485 \pm 0.942	283.178 \pm 0.817
	T	64.333 \pm 0.760	232.667 \pm 0.919	35.000 \pm 0.966	506.333 \pm 1.174	287.667 \pm 0.919	220.333 \pm 1.520
	%	-34.81 *	-53.06 *	-36.93 *	-16.30 *	-27.08 *	-22.19 *
withdrawal 1 week	C	98.688 \pm 0.274	495.653 \pm 1.445	55.493 \pm 0.105	604.906 \pm 2.337	394.485 \pm 0.942	283.178 \pm 0.817
	T	73.667 \pm 0.558	271.333 \pm 1.174	44.000 \pm 0.730	449.570 \pm 7.140	274.333 \pm 1.476	192.333 \pm 0.919
	%	-25.35 *	-45.26 *	-20.71 *	-25.68 *	-30.46 *	-32.08 *

- Statistical analyses were performed between control (C=6) and treated (T=6) animals by using paired *t'* test.

% : Percentage of change from control.

* : Significant at $p < 0.05$.

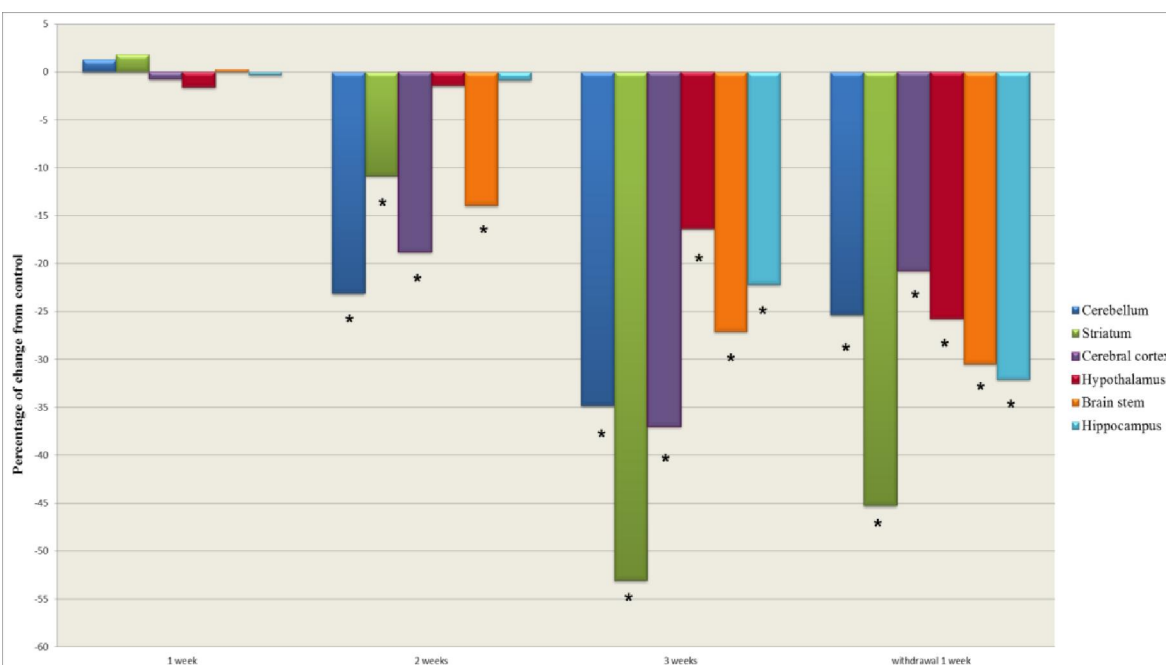


Fig. (1) : Effect of chronic oral administration and Subsequent withdrawal of Red bull (3.1 ml/day) on norepinephrine (NE) content represented by the % difference between control and treated values in the different brain areas of male albino rat

Table (2): Effect of chronic oral administration and Subsequent withdrawal of Red bull (3.1 ml/day) on dopamine (DA) content in the different brain areas of male albino rat.

Time of decapitation		Cerebellum mean \pm S.E.	Striatum mean \pm S.E.	Cerebral cortex mean \pm S.E.	Hypothalamus mean \pm S.E.	Brain stem mean \pm S.E.	Hippocampus mean \pm S.E.
1 week	C	145.648 \pm 0.914	482.312 \pm 3.336	61.240 \pm 0.214	739.237 \pm 4.314	451.541 \pm 1.947	244.597 \pm 1.448
	T	145.446 \pm 0.443	475.888 \pm 5.888	58.868 \pm 1.464	732.001 \pm 3.108	397.000 \pm 0.730	239.515 \pm 3.514
	%	-0.14	-1.33	-3.87	-0.98	-12.08 *	-2.08
2 weeks	C	145.648 \pm 0.914	482.312 \pm 3.336	61.240 \pm 0.214	739.237 \pm 4.314	451.541 \pm 1.947	244.597 \pm 1.448
	T	123.000 \pm 1.095	434.043 \pm 4.145	46.667 \pm 0.760	654.000 \pm 3.795	382.333 \pm 0.919	203.667 \pm 1.282
	%	-15.55 *	-10.01 *	-23.80 *	-11.53 *	-15.33 *	-16.73 *
3 weeks	C	146.755 \pm 0.818	473.948 \pm 0.856	60.488 \pm 0.044	734.223 \pm 2.111	451.288 \pm 0.633	243.147 \pm 0.863
	T	107.000 \pm 0.966	300.300 \pm 1.899	32.000 \pm 0.966	605.000 \pm 1.826	367.667 \pm 0.919	194.000 \pm 1.317
	%	-27.09 *	-36.64 *	-47.10 *	-17.60 *	-18.53 *	-20.21 *
withdrawal 1 week	C	140.527 \pm 6.159	473.948 \pm 0.856	60.488 \pm 0.044	734.223 \pm 2.111	451.288 \pm 0.633	243.147 \pm 0.863
	T	64.500 \pm 1.432	270.270 \pm 0.000	27.667 \pm 0.919	622.667 \pm 1.116	372.667 \pm 0.919	206.333 \pm 1.174
	%	-54.10 *	-42.97 *	-54.26 *	-15.19 *	-17.42 *	-15.14 *

- Statistical analyses were performed between control (C=6) and treated (T=6) animals by using paired *t'* test.

% : Percentage of change from control.

* : Significant at $p < 0.05$.

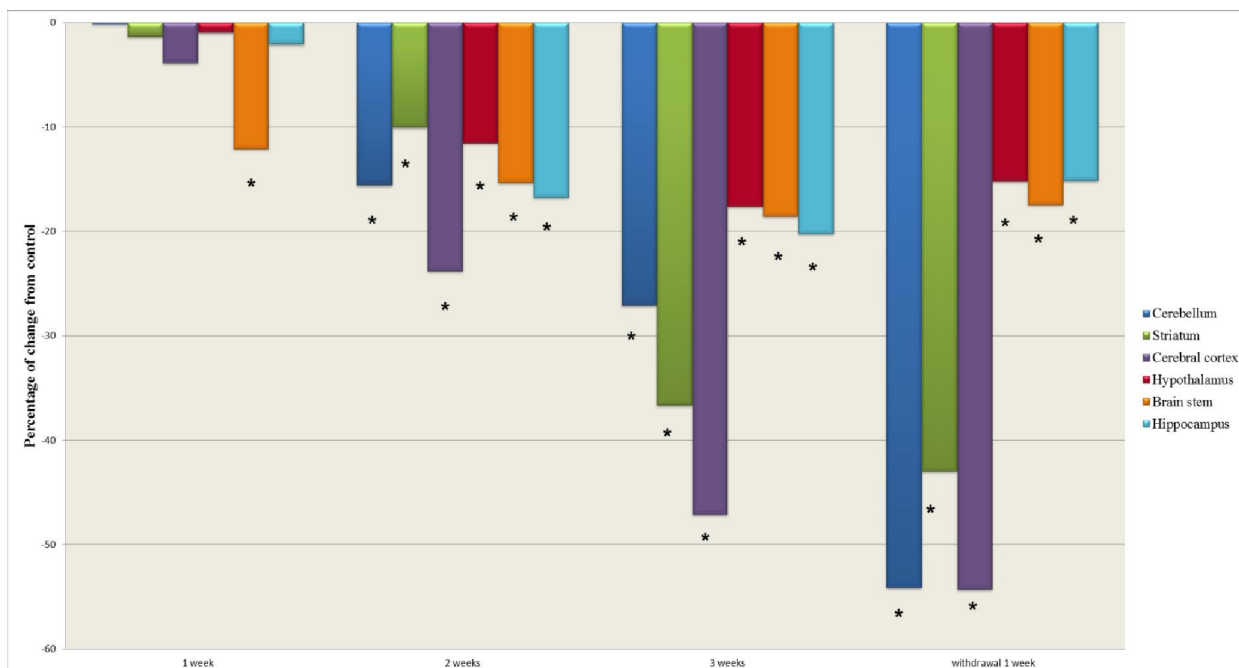


Fig (2) : Effect of chronic oral administration and Subsequent withdrawal of Red bull (3.1 ml/day) on dopamine (DA) content represented by the % difference between control and treated values in the different brain areas of male albino rat .

Table (3): Effect of chronic oral administration and Subsequent withdrawal of Red bull (3.1 ml/day) on gama-aminobutyric acid (GABA) content in the different brain areas of male albino rat.

Time of decapitation		Cerebellum mean \pm S.E.	Striatum mean \pm S.E.	Cerebral cortex mean \pm S.E.	Hypothalamus mean \pm S.E.	Brain stem mean \pm S.E.	Hippocampus mean \pm S.E.
1 week	C	192.457 \pm 0.799	171.652 \pm 0.450	57.247 \pm 0.385	432.828 \pm 0.319	118.155 \pm 0.197	214.787 \pm 1.321
	T	140.667 \pm 0.558	134.000 \pm 2.221	57.000 \pm 0.365	427.729 \pm 2.689	104.333 \pm 1.116	106.333 \pm 2.376
	%	-26.91 *	-21.94 *	-0.43	-1.18	-11.70 *	-50.49 *
2 weeks	C	192.457 \pm 0.799	171.652 \pm 0.450	57.247 \pm 0.385	432.828 \pm 0.319	118.155 \pm 0.197	214.787 \pm 1.321
	T	170.838 \pm 2.706	86.333 \pm 1.647	41.000 \pm 0.365	359.418 \pm 0.748	86.333 \pm 2.231	93.333 \pm 1.174
	%	-11.23 *	-49.70 *	-28.38 *	-16.96 *	-26.93 *	-56.55 *
3 weeks	C	193.611 \pm 0.781	175.423 \pm 1.783	57.849 \pm 0.675	437.968 \pm 1.007	118.436 \pm 0.231	216.865 \pm 0.870
	T	64.333 \pm 1.282	73.667 \pm 1.282	34.333 \pm 1.116	340.226 \pm 0.594	64.000 \pm 1.461	83.333 \pm 1.520
	%	-66.77 *	-58.01 *	-40.65 *	-22.32 *	-45.96 *	-61.57 *
withdrawal 1 week	C	193.379 \pm 0.440	171.744 \pm 1.615	57.713 \pm 0.935	437.849 \pm 0.198	118.118 \pm 1.398	218.139 \pm 2.746
	T	58.667 \pm 0.211	152.000 \pm 2.280	43.667 \pm 1.476	359.307 \pm 1.369	55.000 \pm 0.730	167.333 \pm 0.760
	%	-69.66 *	-11.50 *	-24.34 *	-17.94 *	-53.44 *	-23.29 *

- Statistical analyses were performed between control (C=6) and treated (T=6) animals by using paired *t'* test.

% : Percentage of change from control.

* : Significant at $p < 0.05$.

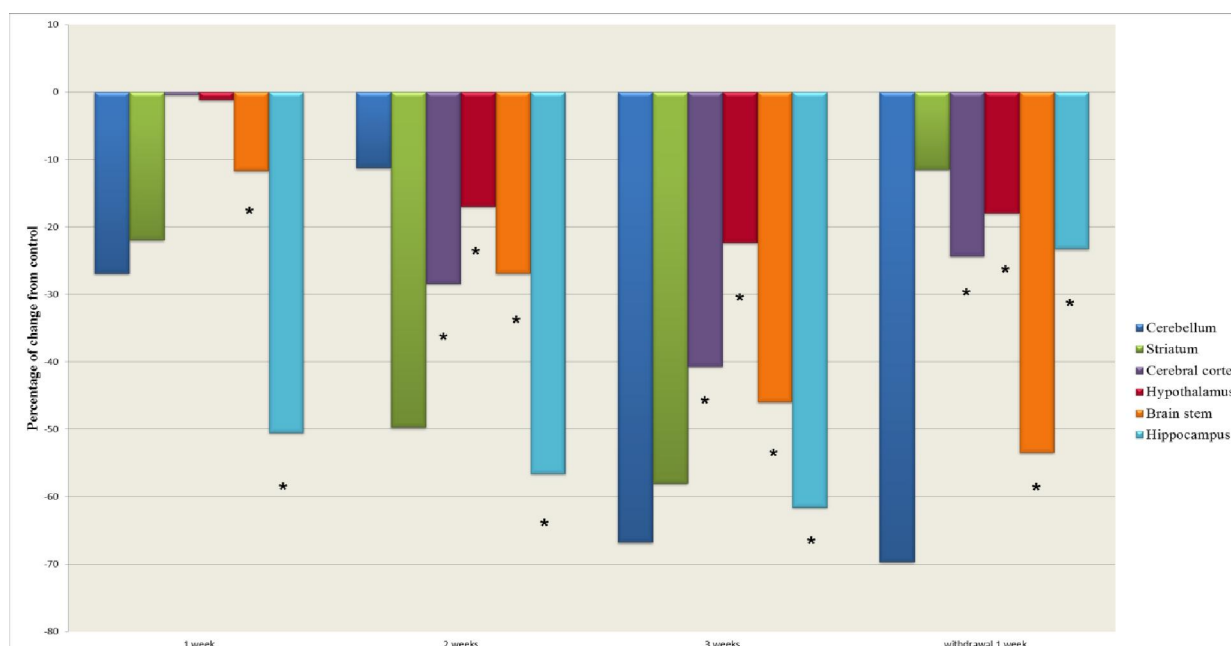


Fig. (3) : Effect of chronic oral administration and Subsequent withdrawal of Red bull (3.1 ml/day) on gama-aminobutyric acid (GABA) content represented by the % difference between control and treated values in the different brain areas of mal

Histopathological Results:

Group 1 (control group)

In the control group, The cerebral cortex was formed of six layers: Molecular layer that have a few neurons fig (4), The Outer granular layer a relatively thin layer consists of a few small crowded neurons fig

(5), the Pyramidal cell layer consists of a hierarchical neurons medium-sized fig (6), Inner granular layer contain a small-sized nerve cells irregularly shaped fig (7), The Ganglionic layer consists of a large pyramidal cells fig (8) and Multi-form cell layer

consist of multiple formats and a small spindle neurons fig (9).

Group 2 (Red Bull group)

The administration of energy drink Red bull for 3weeks result in different histopathological change in cerebral cortex area of rat.

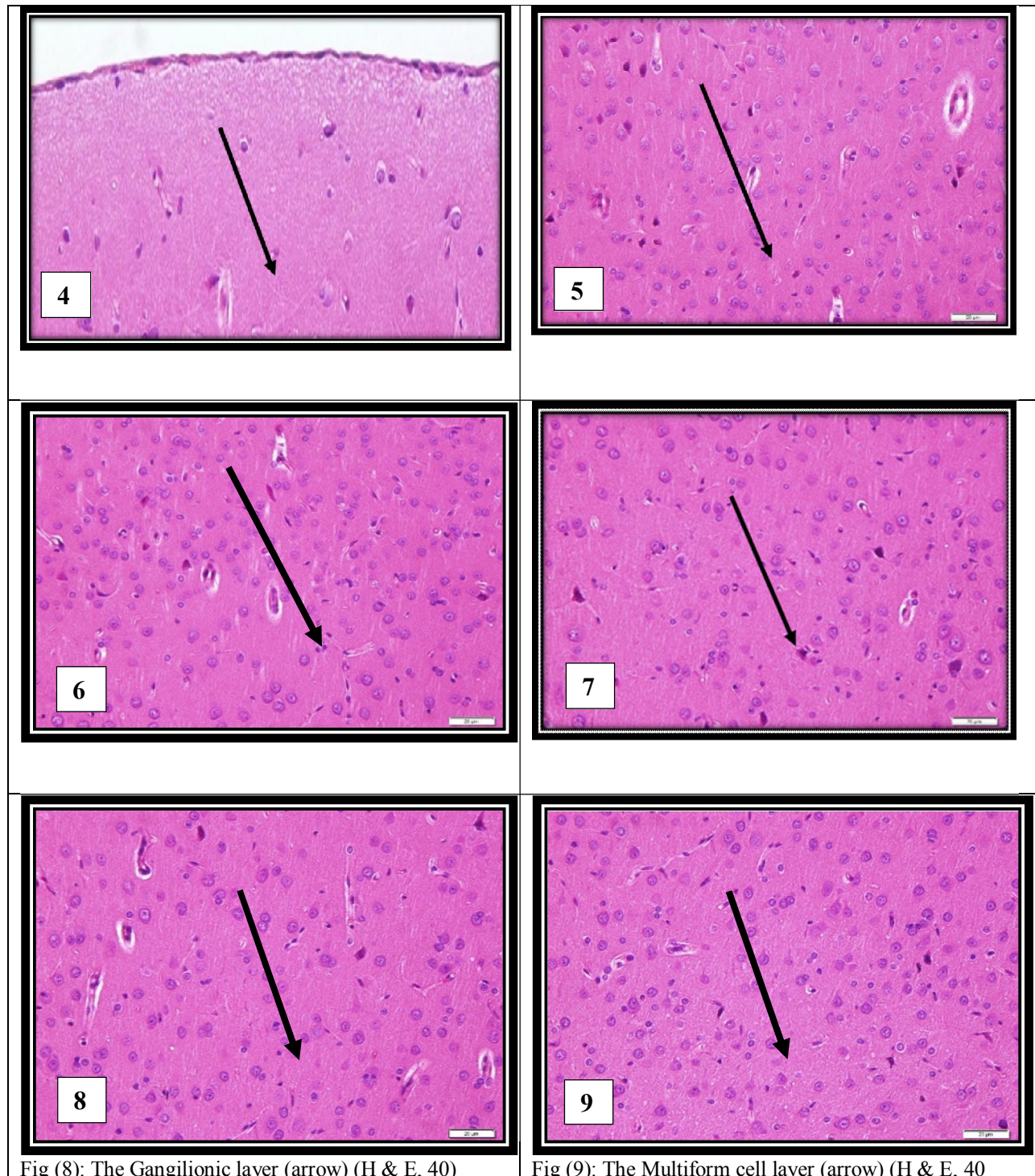


Fig (8): The Ganglionic layer (arrow) (H & E, 40)

Fig (9): The Multiform cell layer (arrow) (H & E, 40)



Figure (10): the molecular layer shows atrophy and neuronal abnormalities and analyzed in neurons (arrow) (H & E X100).

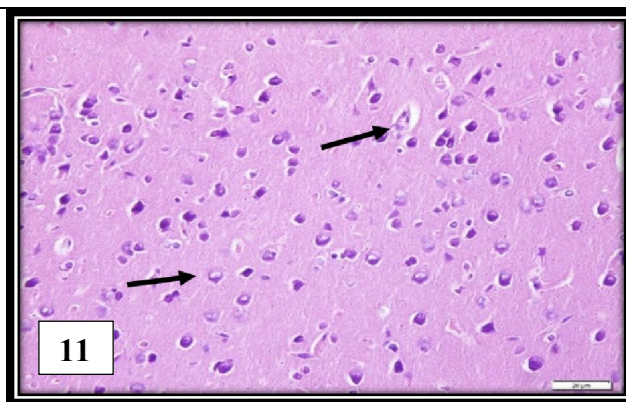


Figure (11): The Outer granular layer shows vacuolated around the nucleus and atrophy nuclei (arrow) (H & E X100).

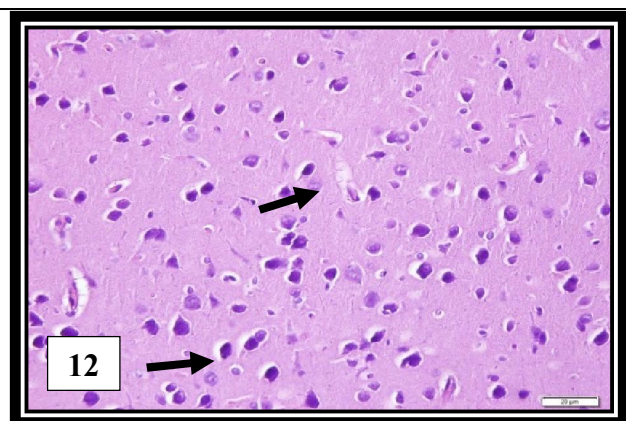


Figure (12): The Pyramidal cell shows the deformation axes neurons and breadth of the breadth vacuolated around the nucleus (arrow) (H & E X100).

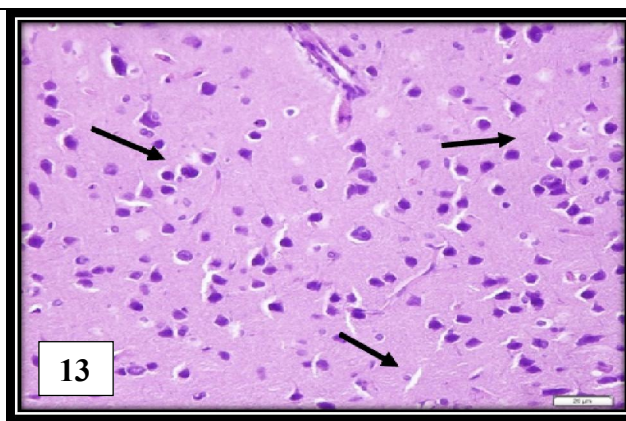


Figure (13): The Pyramidal cell shows a sharp distortion in pyramidal cells and breadth of the blanks around nerve cells and nerve tissue lysis (arrow) (H & E X100).

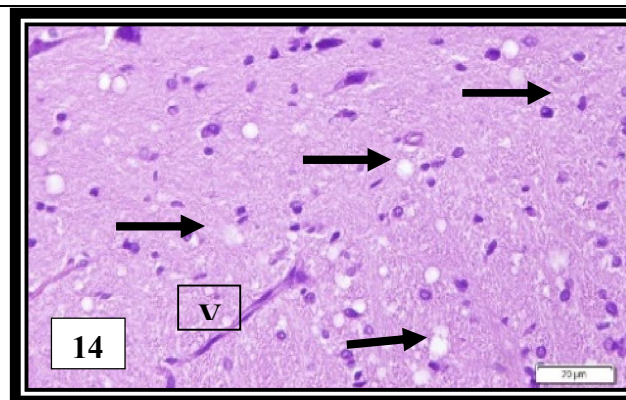


Figure (14): The Inner granular layer show a sharp increase in abnormalities in the blanks in the nervous tissue and analyzed neurons and atrophy and the small number of nerve cells and blood vessel shows clearly in the textile (arrow) (H & E X100).

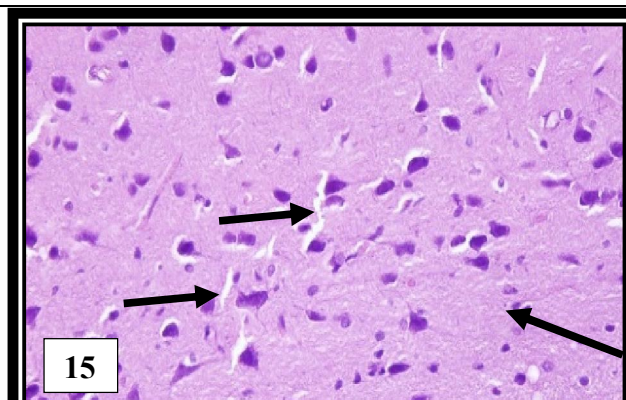


Figure (15): The Inner granular layer where ganglia are spaced from each other and change the shape of the nucleus and become decentralized and change the shape of neuronal body (arrow) (H & E X100).

4. Discussion:

The Result of the current study showed that daily treatment for 3 weeks succession of energy drink Red bull (3.1ml/day) led to a significant decrease in content of neurotransmitter studied (NE, DA and GABA) in most regions of the brain at different times and this is consistent with previous studies which showed that caffeine works to activation producing neurons of noradrenergic, adrenergic, cholinergic, serotonergic and GABAergic increase its release from producing neurons in different brain regions (24). Also, release dopaminergic, which works to increase nerve conduction of dopamine, especially in the mid brain and pons area (25) by increasing release dopamine of the pre-synaptic cells and strengthen the work of its own receptors that lead to occurrence of locomotor activity (26). Using high dose of caffeine lead to release of dopamine-producing cells in brain may have a relationship with symptoms of schizophrenia (27). Caffeine prevented the connector from the link nervous GABA receptors cause stress (28).

Energy drinks contain many ingredients that have a negative effects on the central nervous system such as headache, fatigue (29), increased motor activity, depression, anxiety, sleep disturbances, mood change and irritable (30). The most important energy drinks ingredients caffeine, which have a high ability to cross the blood-brain barrier because its high ability the solubility in lipids (31) which lead to activation the central nervous system and increase motor activity (32), by change the enzyme activity of phosphodiesterase (33) and increase the entry of calcium ions into the ends of nerve cells (34). It was found that caffeine increases the oxidation of fatty acids, which increase the energy and the level of glucose in blood (35).

Caffeine is considered anti adenosine receptors and help reduction the secretion of catecholamines (36). Some studies have shown that the effect of caffeine on the central nervous system may lead to the closure of adenosine receptors and reduces the rate of serotonin into dopamine in the brain and that play an important role in delaying fatigue associated with caffeine intake (37). As a result of the closure of these receptors occur neuroexcitability (38) as a result of reduction of neurotransmitter release (39) leading to a state of alertness and activity associated with the intake of caffeine that found in energy drinks (40).

Caffeine works to close the Adenosine receptors A_1 and A_2 (30) and especially adenosine receptors A_2 in the Striatum area (41) as well as the activation of dopamine receptors in the striatum (42) and thus reduces the activity of cyclic adenosine monophosphate (cAMP), lead to increase a

neurotransmitters that occurred to activity and alertness associated with caffeine abuse (43).

It is known that adenosine from natural components of the cell and increases gradually in the brain during wakefulness and decreases during sleepiness (40). The regulates of adenosine in the body by metabolism Adenosine triphosphate (ATP). Adenosine played an important role in regulating blood flow in the brain (44) as it affects neurotransmission in the brain when activating its receptors (45) where it was worked to prevent irritability nervous and inhibits release of neurotransmitters in the brain, particularly in dopamine, acetylcholine, serotonin, norepinephrine, GABA and glutamate by closed calcium channels and thus prevents the entry of calcium into the nerve cell (46). These changes were accompanied by increasing periods of sleep and inhibition of motor activity and these behavioral manifestations is closely linked to the dopamine and serotonin content in the brain (47).

It has been observed that when taking a low dose of caffeine, it is connected to adenosine receptors A_2 and when taking a high doses that caffeine associated with adenosine receptors A_1 . Moreover, when caffeine bind to adenosine receptors leads to increased secretion of dopamine from producing neurons and expand its release dopamine enhance the work of caffeine (48).

It has been found (45) that during exercise will increases adenosine levels in skeletal muscle, blood and transmitted to the brain. When link the adenosine with receptors work to decrease the level of dopamine in the brain (47) and this reduces the level of serotonin and dopamine that causes, feeling tired and fatigue (49).

Taurine has the ability to cross the blood-brain barrier (51) and worked to protect nerve tissue and has a regulatory role in the transfer of neurotransmitters in the central nervous system. taurine has many important features in the nervous system, it was considered as an Anti-anxiety through interaction with GABA receptors and glycine receptor (52). Taurine works to increase acetylcholine Neurotransmitter in the brain and thus works to reduce the symptoms of Alzheimer's disease (53) and has a role in reducing epileptic seizures by inhibiting the liberation of glutamate neurotransmitter and link GABA receptors (54). It was found from previous studies that taurine increases the production of dopamine and improves locomotor activity (55).

The works of glucose (one of the components of energy drinks) to increase the level of tryptophan in the blood plasma lead to increase of serotonin in the different regions of the brain that have a positive impact on improving mood (56).

Inositol used medically as an anti-depressant by increasing the content of serotonin neurotransmitter (57). The other active compounds in energy drinks such as (evodamine, yohimbine, ginseng) on the liberation of neurotransmitters of dopamine, noradrenaline and adrenaline in the different regions of the brain and the production of neurotransmitters of dopamine and norepinephrine by increasing the amino acid L-tyrosine, one of the components of energy drinks (58).

It was observed during the histological examination of the sectors in the cerebral cortex area for daily treatment of energy drink red bull (3.1ml / day) led to a atrophy of nerve cells and nuclei and abnormalities in pyramidal cells and analyzed the nervous tissue may be due to the effect of caffeine (1).

The results of the current and previous studies it can be concluded that daily treatment of energy drink Red bull lead to the closure of adenosine receptors in order to contain caffeine which causes to open calcium channels and increase the entry of calcium ions into the nerve cell. it was known that neurotransmitters have vesicles associated with endings pre-synaptic cell by a special protein known as protein synapsin 1 and when entering the calcium ions occur phosphorylation of synapsin1 for this protein thus lead to separation of vesicles, release and union with the plasma membrane and exit the content of neurotransmitters via cellular expulsion in the synaptic cleft which leads to a lack of total content inside cells (50).

When the daily treatment of the energy drink led to the regulation adenosine receptors to higher causes to increase the number of adenosine receptors and closing of calcium channels, which worked to increase neurotransmitters content within brain cells, followed by the organization of receptors to the bottom leading to the opening of calcium channels and the entry of calcium ions into the nerve cell, which worked on the decrease of neurotransmitters content within the cells and it was possible that this effect was due to the occurrence probability of caffeine.

Conclusions

The consumption Spread of energy drink between students in Saudi Arabia, which found a significant decrease in neurotransmitter (NE, DA and GABA)in different brain area and its effected negatively on the cerebral cortex that a responsible for organizing the voluntary movements, memory and sensation (emotion). It must be reducing the consumption of energy drink especially on children, adolescents, pregnant and nursing women.

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