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EFFECTS OF VITAMIN B COMPLEX SUPPLEMENTATION ON THE PREFRONTAL CORTEX OF METHAMPHETAMINE-INTOXICATED WISTAR RATS

[1.]Okafor Emeka Christian, [2.]Ezeokafor Emmanuel Nonso,
[3.]Dr Bernard Omuwa Osazuwa, [4.]Dr Akor Ekele Benjamin,
[5.]Nwankwo Samuel Ikwunne, [*6.]Nwanaga Clinton Uche

[1]Anatomy Department, Nnamdi Azikiwe University Awka.

[2]Department of Human Physiology, Nnamdi Azikiwe University,

[3]Anesthesiology Dept. Irrua Specialist/Teaching Hospital, Irrua Edo state.

[4]Department of Human Anatomy, Federal University Lokoja

[5]Department of Zoology, Nnamdi Azikiwe University Awka

[*6]Department of Human Physiology, University of Port-Harcourt

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Abstract: **Methamphetamine (MA) abuse is known to have detrimental effects on brain function, particularly in the prefrontal cortex, resulting in cognitive impairments and neurotoxicity. This study aimed to examine the toxicological effects of methamphetamine on body weight and oxidative stress in rats and evaluate the protective potential of Vitamin B complex supplementation. Seven groups of rats were used: Group A (positive control) received only food and water ad libitum; Group B was induced with a low dose of methamphetamine (2 mg/kg); Group C received a high dose of methamphetamine (10 mg/kg); Group D received a low dose of Vitamin B complex (50 mg/kg); Group E was given a high dose of Vitamin B complex (100 mg/kg); Group F was induced with methamphetamine (10 mg/kg) and treated with a low dose of Vitamin B complex (50 mg/kg); and Group G received methamphetamine (10 mg/kg) along with a high dose of Vitamin B complex (100 mg/kg). Body weight and oxidative stress markers were assessed after the treatment period. Results indicated that methamphetamine-induced groups (B and C) showed significant weight loss and increased oxidative stress, suggesting neurotoxic effects. However, the groups co-treated with Vitamin B complex (Groups F and G) exhibited improvements in body weight and a reduction in oxidative stress, approaching the control group levels. These findings suggest that Vitamin B complex, with its antioxidant properties, may mitigate the neurotoxic effects of methamphetamine. This study highlights the potential of Vitamin B complex as a protective agent against methamphetamine-induced damage to brain function and body weight regulation.**

Keywords: **Methamphetamine, Vitamin B complex, oxidative stress, prefrontal cortex, addiction.**

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1. INTRODUCTION

Mkpuru mmiri, also referred to as ice or methamphetamine (METH), is one of the illegal narcotics most commonly abused by Nigerian youth.

Amphetamines are the second most used illicit drug in the world, second only to cannabis [1]

The use of methamphetamine, or mkpuru mmiri in Igbo, is a common trend at the moment. The teenagers' "Mkpuru mmiri," the name for methamphetamine, means "seed of water." Methamphetamine, sometimes referred to as mkpuru mmiri, is taken by injection of the powder dissolved in water or alcohol, smoking, sniffing, snorting, or swallowing the pill form. [2]

A person's mental condition could be totally destroyed by this psychedelic crystal substance.

Unfortunately, a significant portion of young users suffer as a result. They are now a burden to their families and communities. [3]

There aren't many of these studies, but the ones that have been done in Nigeria have shown how common methamphetamine use is there [4], [2] According to the UNODC [1], 0.1% of participants in the National substance Survey, or 89,000 people, reported using methamphetamine, whereas 0.06% of respondents, or 67,000 people, reported using the substance in the South East. Two of the twelve study participants had taken methamphetamine at some time in their life, according to later research [5].

Consequently, methamphetamine, sometimes referred to as mkpuru mmiri, is a synthetic central nervous system stimulant that is used for a variety of purposes, such as euphoria, improved sexual performance, enhanced alertness, productivity, vigilance, and coping. It is also illegal and highly addictive. (Buxton and Dove, 2018)

Methamphetamine (METH) is a potent psychostimulant known to significantly impact the prefrontal cortex (PFC), a brain region essential for executive functions such as decision-making, impulse control, and working memory. Chronic METH use has been associated with structural and functional alterations in the PFC, leading to cognitive deficits and behavioral impairments.(Guerin et al., 2019)

Research indicates that repeated METH administration enhances inhibitory synaptic transmission onto pyramidal neurons in the PFC. This augmentation is characterized by increased spontaneous and evoked inhibitory postsynaptic currents (IPSCs), heightened GABAergic presynaptic function, and a shift in the excitatory-inhibitory balance favoring inhibition. These changes are mediated, in part, by D1 dopamine receptor signaling pathways. Notably, the intrinsic excitability of parvalbumin-positive fast-spiking interneurons (PV+ FSIs) within the PFC is also elevated following METH exposure. This heightened activity of PV+ FSIs contributes to the observed increase in inhibitory tone, which correlates with working memory deficits. Interventions that modulate PV+ FSI activity have been shown to rescue these cognitive impairments, suggesting potential therapeutic avenues for addressing METH-induced cognitive deficits. (Armenta-Resendize et al., 2022) Emerging research suggests that vitamin B12, a crucial component of the vitamin B complex, may offer neuroprotective benefits against METH-induced brain damage. Studies have demonstrated that vitamin B12 administration can reduce neuronal apoptosis and gliosis in the cerebral cortex, potentially mitigating the neurotoxic effects of METH. Additionally, lower serum levels of vitamin B12 have been observed in METH-dependent individuals, with deficiencies correlating to increased relapse rates and addiction severity. These findings indicate that maintaining adequate vitamin B12 levels might play a role in protecting the PFC from METH-induced neurotoxicity and in improving outcomes for those struggling with METH addiction. [6], [7] Hence, this study aims to investigate the effects of vitamin B complex supplementation on the prefrontal cortex of methamphetamine-intoxicated Wistar rats.

2. MATERIALS AND METHODS

Ethical Clearance

Ethical approval was obtained from the ethical committee, Faculty of Basic Medical Sciences, College of Health Sciences, Nnamdi Azikiwe University, Awka.

Experimental Animals

Twenty-eight (28) adult Wistar rats were procured from Research enterprise farms, University of Ibadan, Oyo state. Perspex cages were used to house group of seven (7) animals for routine experiment. Each cage had wire gauze top for cross ventilation. The animals were allowed for a period of two weeks for acclimatization at the animal house of Anatomy

Department, Nnamdi Azikiwe University, Nnewi Campus, before their weight was taken, under a controlled room temperature of about 25-28°C, relative humidity of about 60-80% and photo-periodicity of 12h day / 12h night. They were fed Ad libitum with water and guinea feed pallets from Agro feed mill Nigeria Ltd. All the animals were treated in accordance with the approval of ethical committee, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institute of Health Guide for the Care and Use of the Laboratory Animals (1985).

Experimental Design:

Group A was the positive Control group, received only food and water ad libitum

Group B was induced with methamphetamine 2mg/kg (low dose)

Group C was induced with 10mg/kg of methamphetamine (high dose)

Group D received 50 mg/kg (low dose) of vitamin B complex.

Group E received 100mg/kg (high dose) of vitamin B complex

Group F was induced with methamphetamine 10mg/kg and treated with vitamin B complex (50mg/kg)

Group G was induced with methamphetamine 10mg/kg and treated with vitamin- B complex (100mg\kg)

Termination of Treatment

The behavioral changes were tested across the seven groups of animals to identify the animals that have lost it motor function. Twenty-four hours after the last exposure, following the behavioral test, the animals were weighed, then anaesthetized under chloroform vapor, and the animal skull dissected by occipitofrontal incision. The brain tissues were harvested from the animals and weighed. The brain tissues of some of the animals were prepared for biochemical analysis through the process of homogenization while the remaining tissues of some of the animals were fixed in 10% Neutral Buffered Formalin for 48hrs and grossed to isolate the brain tissue of interest for histological investigations in the histology laboratory of Anatomy Department, Nnamdi Azikiwe University, Nnewi campus.

Determination of Antioxidant Biomarkers

Malondialdehyde (MDA) estimation 1 ml of serum was heated at pH 3.0 --- 0.1 with 4 ml of saturated TBA reagent in a boiling water bath for 30 min. After the sample has cooled, MDA was estimated from the absorbance of the TBA-MDA complex in the cooled sample at 532 nm [8]

Estimation of superoxide dismutase (SOD)

Superoxide dismutase (SOD) will be investigated with the method described by Kakkar et al. (1984). A total of 650 µl of sodium pyrophosphate buffer will be added to 50 µl of brain supernatant fraction; 50 µl phenazine methosulfate (PMS), 150 µl of nitroblue tetrazolium (NBT), and 100 µl nicotinamide adenine dinucleotide phosphate (NADPH) will be added and the mixture vortexed thoroughly. The reaction mixture will be incubated for 90 s and 500 µl glacial acetic acid will be added to stop the reaction. Two milliliter of n-butanol will be added, vortexes thoroughly. It will be kept at room temperature for 10 min. Absorbance will be measured at 560 nm. The results will be expressed in terms of µmol/min/mg protein [9]

Estimation of reduced Glutathione (GSH)

The measurement was carried out according to the method described by Sedlak and Lindsay (1968) with slight modifications, using the serum samples. The principle was dependent on protein precipitation using tungstate/sulfuric acid solution and yellow coloration formation after reaction with 5, 5′dith-iobis-2-nitrobenzoic acid (DTNB), and the absorbance was read within 30–60s at 412nm against the blank. Glutathione (GSH) concentrations were extrapolated from a standard GSH curve.[10]

Tissue Processing and Immunohistochemical Staining Protocol for Histological Analysis

The tissue processing protocol was based on methods by Drury and Wallington (1980). Tissues were fixed in 10% Neutral Buffered Formalin for 48 hours, washed, dehydrated in increasing alcohol concentrations, cleared in xylene, and infiltrated with paraffin wax at 60°C. Sections were stained with Hematoxylin and Eosin, dehydrated, cleared, and mounted.[11]

For MBP and Olig2 staining, antigen retrieval was done with a citrate-based solution, followed by primary antibody incubation (anti-MBP, anti-Olig2) and HRP detection. Sections were counterstained, dehydrated, cleared, and mounted.

Photomicrographs were taken at 400x magnification and analysed using Image software.

Data Analysis

Data was analyzed using SPSS version 27.0.1 software package. Mean and standard deviation were obtained and one-way analysis of variance (ANOVA0 was used to compare values between groups. Data was expressed as Mean ± Standard Deviation (SD) and then considered statistically significant when P ≤0.05.

3. RESULTS

Table 1: Effect of Morphometric Analysis of Body Weight

GROUPS	WEIGHT (g)	MEAN± SEM	p-value
GROUP A	Initial Final	150.00±0.00 175.43±0.42	0.001
GROUP B	Initial Final	153.07±0.12 148.12±0.05	0.009
GROUP C	Initial Final	148.01±0.08 137.65±0.32	0.003
GROUP D	Initial Final	149.42±8.50 164.85±0.00	0.000
GROUP E	Initial Final	151.33±3.74 168.66±0.03	0.003
GROUP F	Initial Final	143.84±2.65 161.25±6.43	0.005
GROUP G	Initial Final	149.38±1.31 169.30±0.54	0.002

Data was analyzed using Student Dependent *T-test and values were considered significant at P<0.05*

Body weight changes:

A significant decrease in final body weight was observed in groups B and C when compared to their corresponding initial body weights. A significant increase was recorded in control group A, with all other groups (in groups D and E, F, G)

OXIDATIVE STRESS BIOMARKERS

	Groups	Mean ± SEM	p-value	F-value
MDA (mm^{-1})	**Group A**	3.51± 0.01		33.545
	Group B	3.67± 0.01	0.002	
	Group C	3.86± 0.06	0.000	
	Group D	3.51±0.29	0.000	
	Group E	3.51±0.03	0.000	
	Group F	3.57±0.01s	0.001	
	Group G	3.53±0.00	0.001	

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Data were analyzed using One-way ANOVA, followed by Post HOC Fisher's LSD multiple comparison, and data was considered significant at P<0.05

The control group (Group A) exhibited a mean malondialdehyde (MDA) level of 3.51. Statistical analysis indicates that Group B experienced a significant increase in mean MDA levels compared to the control group ($p < 0.002$). Groups C, D, E, F, and G showed mean MDA levels similar to the control.

GSH (mm^{-1})	**Group A**	1.62 ± 0.02		**12.432**
	Group B	1.56 ± 0.03	0.001	
	Group C	1.45 ± 0.02	0.002	
	Group D	1.62 ± 0.20	0.001	
	Group E	1.62±0.01	0.000	
	Group F	1.61±1.32	0.015	
	Group G	1.63±0.21	0.020	

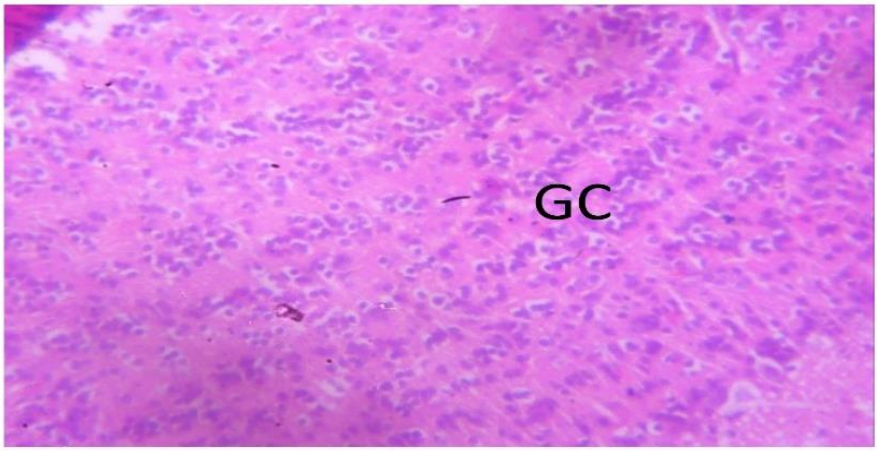
The control group (group a) exhibited a mean glutathione (GSH) level of 1.62. statistical analysis revealed that groups b ($p = 0.001$) and c ($p = 0.002$) experienced significant decreases in mean GSH levels compared to the control group. groups d ($p = 0.001$), e ($p < 0.001$), f ($p = 0.015$), and g ($p = 0.020$) showed mean GSH levels similar to the control.

SOD (mm^{-1})	**Group A**	8.24 ± 0.02		1583.643
	Group B	8.13 ± 0.02	0.000	
	Group C	7.43 ± 0.03	0.000	
	Group D	8.24 ± 0.34	0.000	
	Group E	8.24 ± 0.21	0.000	
	Group F	7.95± 0.13	0.005	
	Group G	8.34 ± 0.03	0.020	

The control group (Group A) exhibited a mean superoxide dismutase (SOD) level of 8.24. Statistical analysis indicates that Groups B ($p < 0.001$), C ($p < 0.001$), and F ($p = 0.005$) experienced significant decreases in mean SOD levels compared to the control group, while Group G ($p = 0.020$) showed a significant increase. Notably, Groups D and E had mean SOD levels identical to the control.

MDA= Malondialdehyde, GSH= gluthathione, SOD= superoxide dismutase

HISTOLOGY:



Photomicrograph of GP A Control section of prefrontal cortex shows prefrontal cortex with active and distinct prymaidal cells

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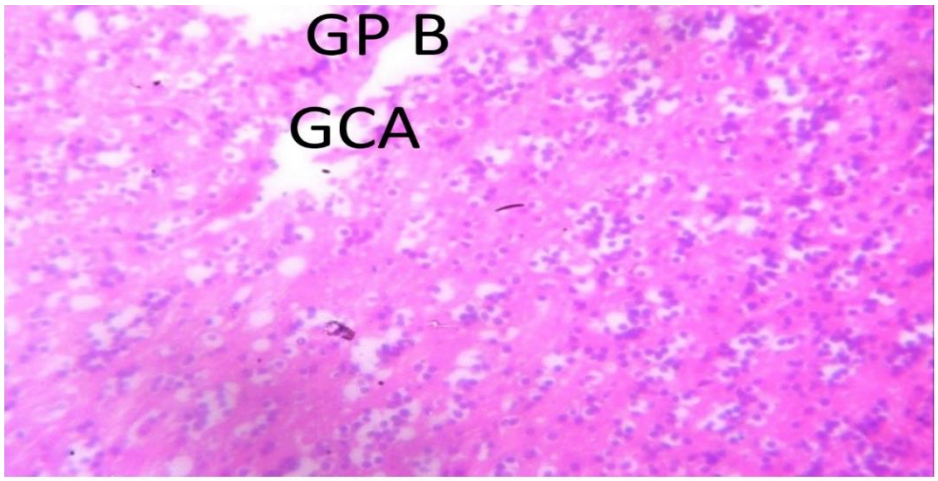
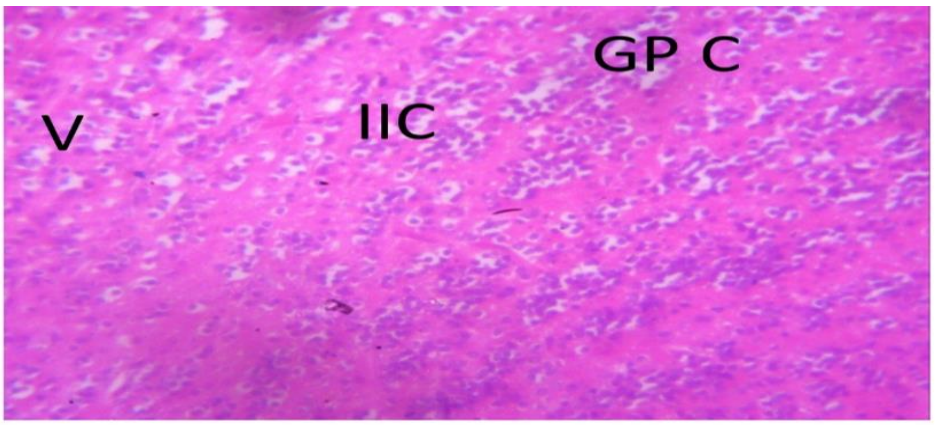
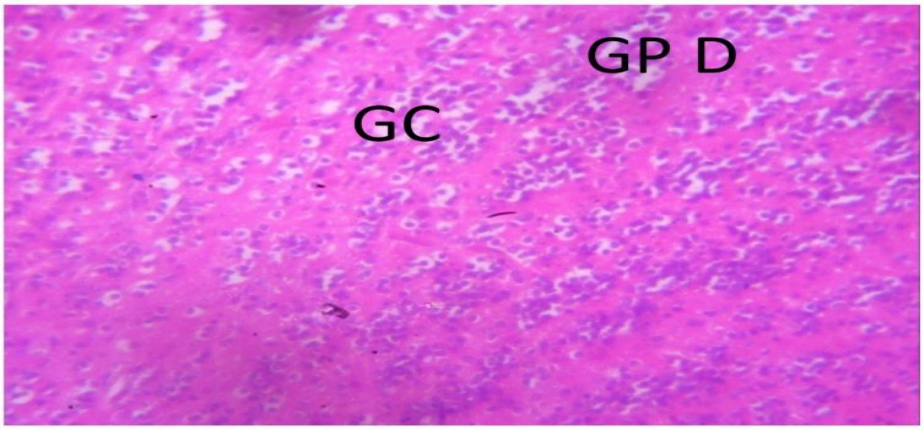


Photomicrograph of group B section of pefrontal cortex of an adult wistar rat induced with methamphetamine 2mg/kg (low dose) only **shows moderate degeneration with moderate granular cell attroph (GCA)**



Photomicrograph of group C section of prefrontal cortex of an adult wistar rat induced with 10mg/kg of methaphetamine (high dose) **shows mild regeneration with severe focal area of hemorrhage (H) and moderate cluster of inflammatory cells (CIC)**



Photomicrograph of group D section of prefrontal cortex of an adult wistar rat administered with 50mgkg of of vit B complex **shows mild active granular cell**

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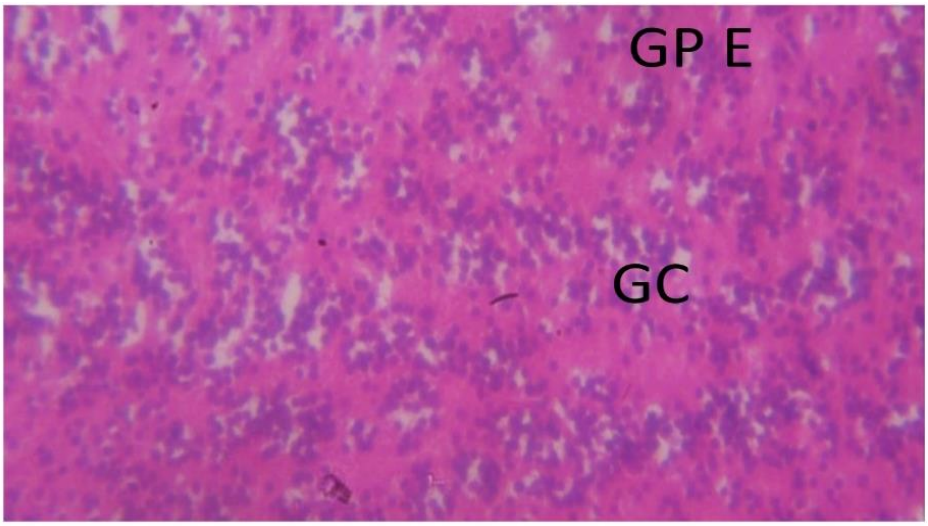
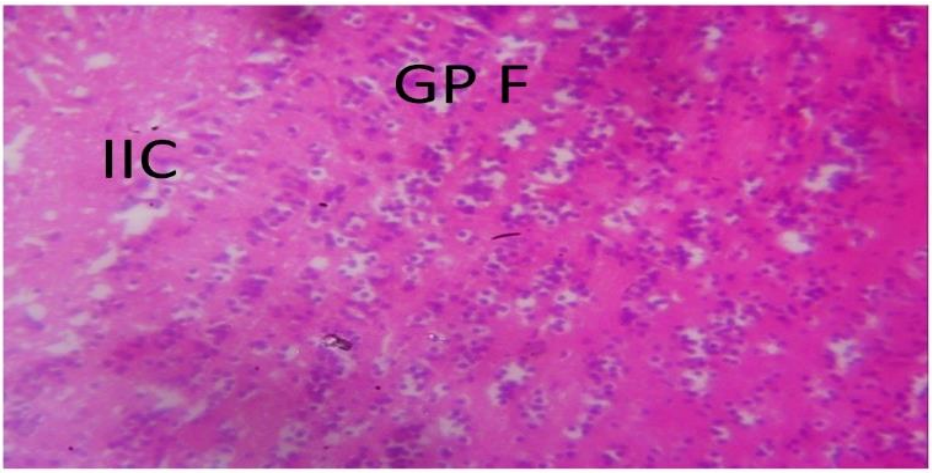


Photomicrograph of group GP E section of prefrontal lobe (x100x400)(H/E) shows adULT wistar administered (high dose) vitamin B shows **prefrontal lobe with active granular cells (GC)**



Photomicrograph of group GP F section of prefrontal lobe of adult wista rat induced with metha 10mfkm and treated with vitamin B complex 50mg/kg **(x100x400)(H/E) show moderate Regeneration with mild infilteration of inflammatory cell (IIC) .**

4. DISCUSSION

Methamphetamine has toxicological effect on the brain. Studies on the toxic effect have been reported by national institute on drug abuse (NIDA) and the United States Drug Enforcement Administration (DEA) on August 2011. They report that methamphetamine abuse has many negative consequences, including addiction. (Addiction is a chronic, relapsing disease, characterized by compulsive drug seeking and use and accompanied by functional and molecular changes in the brain).

administered methamphetamine, compared to the control group. Methamphetamine is a well-known appetite suppressant in animals, as reported by Kuhn, Cynthia, Swartzwelder, and Wilson (1998).

According to the National Survey on Drug Use and Health, methamphetamine use is associated with rapid weight loss, heightened libido, and intense feelings of alertness and concentration. Its effects on the cardiovascular system include increased blood pressure, vascular weakening, and damage to veins, arteries, and capillaries within the central nervous system. These changes elevate the risk of clot formation, vascular scarring, and ultimately, an increased likelihood of stroke, which may contribute to reduced blood volume in the body.

Those that were treated with vitamin B complex only, methamphetamine high dose + Vitamin B complex low dose and those treated with methamphetamine high dose with vitamin B complex high dose shows significant increase in body weight similar with the control group. Vitamin B complexes are known for their unique function in aiding to convert carbohydrates, fats, and proteins into energy. Adequate energy supports the physical activity levels, which is essential for maintaining a healthy weight. It also regulates appetite. B vitamins, particularly B1 (thiamine), B2 (riboflavin), and B6 (pyridoxine), are involved in the regulation of appetite. A deficiency might lead to decreased appetite, while adequate levels can help maintain a healthy appetite. B vitamins are essential for various metabolic processes. A well-functioning metabolism can help manage weight effectively (Ohta, et al., 2020).

Groups G and F despite being administered with methamphetamine still have the relative body weight similar with the control group A, this is due to the vitamin B complex having the property to boost appetite and are very beneficial to the immune system. Vitamin B supplements was able to fight the appetite-suppressant effects of methamphetamine.

The levels of oxidative stress in Groups D and E are comparable to those in the control group (Group A). Oxidative stress is characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses, leading to potential cellular damage.

Groups B and C exhibit significantly higher oxidative stress compared to those receiving vitamin B complex. Amphetamine-type stimulants, which readily cross the blood-brain barrier, act as sympathomimetic agents that stimulate the central nervous system (CNS) by increasing synaptic dopamine (DA) and serotonin (5-HT) availability. While these are the acute effects of methamphetamine (MA), prolonged exposure can lead to neurotoxicity and long-term damage to dopaminergic axon terminals.

The elevated DA levels in Groups B and C undergo auto-oxidation, generating toxic ROS such as hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH\cdot$), and superoxide radicals ($O_2\cdot^-$). These ROS contribute to oxidative damage of proteins, lipids, DNA, and RNA in Groups B and C, as they lack sufficient antioxidant or enzymatic detoxification mechanisms (Kate and Kelly, 2017).

In contrast, oxidative stress levels in Groups F and G are slightly similar to those in the control group (Group A), likely due to the protective effects of vitamin B complex, which facilitates detoxification and counteracts oxidative damage.

5. CONCLUSION

Methamphetamine has a negative effect on the prefrontal cortex of the brain which include cerebral stroke, hemorrhage, psychoses, seizures etc.

Methamphetamine use results in massive releases of the neurotransmitters norepinephrine and dopamine (along with other neurotransmitters) that lead to a number of extremely powerful euphoric effects, increases in energy, feelings of invulnerability, and other psychoactive effects. Because the substance is often made with a number of other substances that are potentially toxic, such as antifreeze, battery acid etc.

The findings of this study suggest that vitamin B complex can act as antioxidants and protect an individual from toxicological effect of methamphetamine.

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