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Effects of Methamphetamine Exposure on Lipid Profile and Cardiovascular Risk in Wistar Rats

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ABSTRACT: Methamphetamine (METH) is a highly addictive psychostimulant that not only impacts the central nervous system but also poses significant risks to metabolic and cardiovascular health. This study investigates the chronic effects of METH on the lipid profile and cardiovascular risk in Wistar rats using appropriate standard method. Data obtained show that methamphetamine induced significant weight loss in the high dose group (from 0.46 to 0.39 g/cm^2). The lipid profile result (table 2) indicated reduction in cholesterol (CHOL), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels with higher doses, while triglycerides (TG) increased. The findings revealed that chronic METH intake led to a dose-dependent reduction in body mass index (BMI) and significant alterations in lipid parameters. These suggest that METH alters lipid metabolism, potentially contributing to increased cardiovascular risk in chronic users.

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Methamphetamine (METH), commonly known by street names such as “crystal meth” or “ice” is a powerful psychostimulant that is notorious for its high potential for abuse and dependence (Kish, 2008). It is a powerful, highly addictive stimulant that affects the central nervous system. It takes the form of a white, odorless, bitter-tasting crystalline powder that easily dissolves in water or alcohol (Chomchai and Chomchai, 2015). It can be smoked, snorted, injected, or taken orally (Gonzales *et al.*, 2010). It is classified as a Schedule II drug, indicating its legal medical use for certain conditions but also its high risk of addiction (Kish, 2008). Over the past few decades, methamphetamine abuse has surged globally, raising significant concerns due to its detrimental impact on human health (Gonzales *et al.*, 2010). Compared with other stimulants (e.g., cocaine and nicotine) the half-life of METH is quite long, ranging from 8 to 12 hours (Gonzales *et al.*, 2010). Access and availability are major contributors to the problem as METH is manufactured using readily available retail products (e.g., pseudoephedrine, hydrochloric acid, red phosphorus, ether, etc.) and numerous “recipes” on how to produce METH are widely available on the internet (Gonzales *et al.*, 2010). Beyond its well-known neurological effects, METH exposure has been increasingly linked to metabolic disruptions, particularly alterations in lipid metabolism, which in turn may elevate cardiovascular risk (Kim *et al.*, 2019). Given the rising prevalence of methamphetamine use, understanding its broader physiological effects, including on lipid profile and cardiovascular health, is critical. The lipid profile, consisting of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), plays a vital role in cardiovascular risk assessment (Orozco-Beltran *et al.*, 2017). An imbalance in these lipid parameters is a significant predictor of atherosclerosis, hypertension, and other cardiovascular diseases (CVDs). Methamphetamine-induced dyslipidemia, a condition marked by abnormal lipid levels, has

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garnered research attention in recent years, as it may contribute to the increased cardiovascular morbidity seen in chronic methamphetamine users (Kevil *et al.*, 2019). Animal models, particularly Wistar rats, have become instrumental in dissecting the physiological and biochemical changes associated with drug exposure (Mukherjee *et al.*, 2022; Spanagel, 2017). Wistar rats are commonly used in biomedical research due to their well-characterized physiology, making them ideal for studying drug-induced metabolic and cardiovascular alterations (Ghezzi *et al.*, 2012). Numerous studies have shown that METH exposure in rodents can lead to oxidative stress, inflammation, and systemic toxicity, which may collectively contribute to cardiovascular dysfunction (McDonnell-Dowling and Kelly, 2017). However, specific investigations into the effects of methamphetamine on lipid metabolism in Wistar rats, and its relationship to cardiovascular risk, remain limited.

This objective of this paper is to evaluate the impact of chronic methamphetamine exposure on lipid profiles and cardiovascular risk in Wistar rats.

MATERIALS AND METHODS

Reagents and Chemicals: All reagents and chemicals used were of analytical grade.

Animal Model: The Wistar rats (weighing between 100g-150g) used were obtained from a reputable breeding facility (Animal House of the Faculty of Basic Medical Sciences, Delta State University, Abraka) to ensure uniformity in genetic background. The Wistar rats were housed in standard animal cage and maintained under controlled environmental condition with a 12h dark: light cycle. They were acclimatized for two weeks before the commencement of experiments and the rats were given free access to feed and water *ad libitum.* During the experimental period, animals were administered with Methamphetamine in different doses. In this study, all the animal experimentation was carried out according to the guidelines of Institutional Animal Ethics Committee (IAEC).

Methamphetamine: Pharmaceutical-grade methamphetamine was utilized to maintain consistency and purity. Dosage levels was determined based on previous studies (Koriem and Soliman, 2014) and was aimed at mimicking chronic human exposure patterns (chronic exposure was achieved through daily oral administration). METH was dissolved in saline and prepared fresh every day for oral administration.

Experimental Design: Rats were randomly divided into control and methamphetamine-exposed groups. The methamphetamine-exposed group received daily doses of methamphetamine orally to simulate chronic intake. They were 4 groups of 4 rats each as follows.
Group 1: Normal control rats were solely maintained on standard chow diet and water *ad libitum* for Six weeks; no induction of methamphetamine.
Group 2: Methamphetamine (5 mg/Kg/day) was administered to rats for 4 weeks--Low dose group.
Group 3: Methamphetamine (10 mg/Kg/day) was administered to rats for 4 weeks – Medium dose group.
Group 4: Methamphetamine (20 mg/Kg/day) was administered to rats for 4 weeks--High dose group.

Collection of tissues: At the end of the four-weeks exposure period, the animals were fasted for 12 hours before being sacrificed by cervical decapitation. A laparotomy was performed to expose the internal organs, and blood samples were collected by cardiac puncture using a hypodermic syringe and needle. The collected samples were placed in plain tubes. The blood samples were centrifuged at 4000 rpm for 15 minutes, and the serum obtained was stored at 4°C for subsequent assays.

Assessment of Lipid Profile: The level of HDL and LDL cholesterol in plasma were determined by the method of Castelli *et al.*, (1977). The level of triacylglycerol in plasma was determined by the method of Fossati and Prencipe, (1982).

Data Analysis: Statistical analysis was conducted using one-way analysis of variance (ANOVA) to determine significant differences between control and methamphetamine-exposed groups.

RESULTS AND DISCUSSION

Effect of Chronic Intake of Methamphetamine on rat weight: The effect of chronic intake of methamphetamine on BMI can be seen in table 1.

Table 1: effect of chronic intake of methamphetamine on body mass index

Groups	Body-Mass Index (g/cm^2)		
	A	**B**	**C**
1	0.45 ± 0.03	0.47 ± 0.04	0.48 ± 0.05
2	0.46 ± 0.03	0.45 ± 0.04	0.44 ± 0.05
3	0.45 ± 0.03	0.43 ± 0.04	0.41 ± 0.05
4	0.46 ± 0.03*	0.42 ± 0.04	0.39 ± 0.05

All values are expressed as Mean ± Standard Deviation (n=4). Value containing the superscript symbol (*) on the same row is statistically different ($p<0.05$).
Key: BMIs 1 – 3 represent Body-Mass Index calculated before induction of Methamphetamine, 2 weeks after commencement of Methamphetamine induction, after 4 weeks induction of Methamphetamine/before sacrifice

Result shows that in Group 1 (Control), there was a steady increase in BMI over time. Group 2 (Low dose) experienced a slight decrease in BMI from week 2 to

week 4. In Group 3 (Medium dose), there was a noticeable decrease in BMI over time. Group 4 (High dose) showed a significant decrease in BMI, especially from week 2 to week 4. The results indicate that chronic intake of methamphetamine leads to a dose-dependent reduction in BMI, with the high dose group showing the most significant decrease.

Effect of Chronic Intake of Methamphetamine on Lipid profile markers: Table 2 reveals the effect of chronic intake of methamphetamine on lipid profile markers. It depicts that cholesterol (CHOL) levels decreased significantly with higher doses. Triglycerides (TG) increased with increasing dose. High-density lipoprotein (HDL), commonly known as good cholesterol, decreased significantly ($p < 0.05$) in the medium and high dose group. Low-density lipoprotein (LDL), or bad cholesterol, decreased significantly ($p < 0.05$) with increasing doses.

Table 2: effect of chronic intake of methamphetamine on lipid profile markers

GROUP	CHOL	TG	HDL	LDL
1	92.50 ± 12.66^{a}	33.05 ± 11.75^{a}	18.15 ± 3.18^{a}	67.74 ± 11.73^{a}
2	87.23 ± 18.64^{b}	39.93 ± 15.83^{b}	18.15 ± 3.91^{a}	61.09 ± 12.69^{b}
3	71.20 ± 9.35^{c}	51.43 ± 28.75^{c}	13.50 ± 2.56^{b}	48.41 ± 8.14^{c}
4	63.65 ± 20.37^{d}	53.10 ± 29.98^{c}	11.30 ± 2.95^{b}	39.74 ± 21.81^{d}

All values are expressed as Mean ± Standard Deviation (n =4). Values containing a similar figure or alphabet superscripts on the same row or column respectively, are statistically the same (p>0.05).

Methamphetamine (METH) is a potent psychostimulant that primarily acts on the central nervous system by facilitating the excessive release of monoamines, such as dopamine (DA), norepinephrine (NE), and serotonin (5-HT), from presynaptic neurons. This dysregulation of neurotransmitter systems contributes to its highly addictive properties and wide range of physiological effects. Chronic METH exposure is known to induce significant biochemical alterations, particularly within the metabolic and cardiovascular systems. By overstimulating dopaminergic pathways, METH leads to a cascade of events that interfere with key metabolic processes, including appetite regulation, lipid homeostasis, and energy expenditure (Yasaei and Saadabadi, 2023). The resultant neurochemical disturbances may initiate alterations in lipid metabolism, influencing the synthesis, transport, and oxidation of lipids, and potentially contributing to cardiovascular pathologies such as dyslipidemia and atherosclerosis.

The results presented highlight the impact of chronic methamphetamine (METH) intake on body mass index (BMI) and lipid profile markers in rats, reflecting a dose-dependent influence on these physiological parameters. BMI is a numerical value derived from an individual's weight and height, used as a screening tool to categorize individuals into different weight status categories (Khanna *et al.*, 2022). The chronic intake of methamphetamine led to a progressive reduction in BMI across all treatment groups compared to the control. Group 1 (Control) showed a steady, consistent increase in BMI over time, indicating normal weight gain in rats that were not exposed to methamphetamine. In contrast, Group 2 (Low dose, 5 mg/kg) demonstrated a slight decrease in BMI, particularly after week 2, suggesting a mild interference with normal weight gain, but not as profound as the higher-dose groups. Group 3 (Medium dose, 10 mg/kg) experienced a more noticeable reduction in BMI over the experimental period, while Group 4 (High dose, 20 mg/kg) displayed a significant decrease in BMI, especially between weeks 2 and 4. This dose-dependent reduction in BMI suggests that methamphetamine induces anorexic effects by altering central nervous system pathways involved in appetite regulation, energy balance, and metabolic rate (Hopkins and Blundell, 2017). The highest dose caused the most severe reduction in BMI, likely reflecting methamphetamine's capacity to suppress feeding behavior and increase energy expenditure through heightened locomotor activity (Hwang *et al.*, 2023).

Methamphetamine exposure also had a pronounced effect on lipid profile markers. The results showed a significant decrease in cholesterol (CHOL) levels with increasing doses, most notably in the high-dose group. Cholesterol is essential for maintaining membrane fluidity and as a precursor for steroid hormones (Craig *et al.*, 2023), but methamphetamine's impact on lipid metabolism, possibly via increased oxidative stress and impaired hepatic function, may explain the observed reduction. Triglycerides (TG) increased with higher doses of methamphetamine, reflecting disrupted lipid metabolism, which may result from increased lipolysis and subsequent release of free fatty acids into the bloodstream, typical in stress-induced conditions (Edwards and Mohiuddin, 2023). Furthermore, high-density lipoprotein (HDL), often regarded as "good" cholesterol due to its role in reverse cholesterol transport (Vergeer *et al.*, 2010), decreased significantly in the medium and high-dose groups. The reduction in HDL could contribute to an increased risk

of cardiovascular diseases. Similarly, low-density lipoprotein (LDL), commonly known as "bad" cholesterol due to its tendency to deposit in arterial walls (Pappan *et al.*, 2024), also decreased significantly with increasing doses. While a reduction in LDL might appear beneficial, this result might indicate methamphetamine's general suppression of lipid synthesis pathways, which disrupts normal lipid homeostasis. Overall, these findings suggest that chronic methamphetamine intake induces significant alterations in both BMI and lipid profiles, potentially increasing the risk of metabolic disturbances, cardiovascular diseases, and other related health issues.

Conclusion: Chronic intake of methamphetamine significantly influences body mass index and lipid metabolism in a dose-dependent manner, as observed in Wistar rats. The reduction in cholesterol and high-density lipoprotein (HDL) levels, alongside the increase in triglycerides, indicates a potential elevation in cardiovascular risk, particularly in individuals with prolonged exposure to methamphetamine. These findings underscore the need for further research into therapeutic interventions aimed at mitigating the cardiovascular complications associated with chronic methamphetamine use.

Conflict Of Interest: The authors declare no conflict of interest.

Data Availability Statement: Data are available upon request from the corresponding author.

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