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Research Article

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Impact of Nicotine Exposure and Withdrawal on Plasma Glucose, Insulin and Glycated Haemoglobin in High-fat Diet Fed Wistar Rats

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Abstract

Background to the Study: *Nicotine, which is the most abundant constituent of tobacco cigarette is one of the most commonly abused drugs. The duo of obesity and tobacco smoking increases the risk of cardiometabolic disorders.*

Methodology: *The experiment involved 48 male waster rats separated into 4 groups of 8 rats each. All the animals were placed on high-fat diet (Margarine; blue band) in addition to the different doses of nicotine in the experimental groups. Group 1 served as control and received distilled water, Groups 2, 3 and 4 received 200µg/kg, 400µg/kg and 800µg/kg of nicotine oral solution respectively. The experimental groups were placed on their respective doses of nicotine solution for an initial four weeks. Thereafter, four animals in each group were sacrificed and blood samples collected to determine their nicotine exposure plasma levels of glucose, insulin and glycated hemoglobin. The remaining four animals in each group continued without nicotine for another four weeks after which they were sacrificed and blood samples collected to determine their nicotine withdrawal plasma levels of glucose, insulin and glycated hemoglobin.*

Results: *The results showed that exposure to the three concentrations of nicotine (200, 400 and 800µg/kg respectively) significantly caused a rise in plasma insulin levels but dose-dependent reduction in both glucose and glycated haemoglobin compared to their control groups. Four weeks after withdrawal of initial 200µg/kg nicotine there were no significant changes in the levels of plasma glucose, insulin and glycated haemoglobin compared to the nicotine exposed groups. Withdrawal, after initial exposure to 400µg/kg of nicotine was associated with significant rise in both the plasma glucose and glycated haemoglobin but no significant change in insulin compared to their respective nicotine exposed groups. Cessation, after initial exposure 800µg/kg of nicotine resulted in significant rise in plasma levels of glucose, glycated haemoglobin and insulin compared to their nicotine exposed groups.*

Conclusion: *The possible reduction in food consumption and increased physical activity together with the increased levels of insulin in the plasma could contribute to the lowered plasma glucose shown in this study. The reduction in the levels of glycated haemoglobin following exposure to nicotine may be potentially beneficial in diabetic management. Therefore, reversal of plasma glucose and glycated haemoglobin levels could be achieved four weeks after cessation of 800µg/kg of nicotine. This result could suggest a possible association of nicotine cessation with decreased insulin sensitivity.*

Keywords: Nicotine, Plasma Glucose, Insulin, Glycated Haemoglobin, High-Fat Diet

Introduction

The global prevalence of cigarette smoking has remained unabated over the years despite all the campaigns staged against it [1]. Studies have associated higher risk of cardiovascular disorders and other conditions with cigarette smoking [2]. Although some studies suggest that combining exercise or dietary factors could mitigate the risk of disease in cigarette smokers, it has remained a leading cause of preventable death globally [3-5]. The most abundant constituent of tobacco cigarette is nicotine which has proven addictive effect on smokers, making it one

of the most commonly abused drugs [6, 7]. Nicotine binds to nicotinic cholinergic receptors to stimulate the release of dopamine and thus adrenaline [8, 9]. The drug has significant effects on attention and memory [10, 11]. However, sudden withdrawal of nicotine has been associated with reversible impairment of attention and memory [12].

Obesity, a global epidemic and major public health concern is basically characterized by excessive body fat accumulation. Comparatively, the prevalence of obesity amongst smokers is lower than that of non-smokers [13]. Although, obesity alone is associated with increased risk of cardio-metabolic disorders. However, obesity paired with tobacco smoking further increases the risk of cardio-metabolic disorders and represent the largest challenges to public health [14, 15]. The causal correlation between nicotine and obesity is poorly understood, thus necessitating this study. Eating and smoking are behavioural traits that are to an extent controlled by the same reward mechanism [16]. Studies have shown that nicotine may interfere with glucose-regulating mechanisms of the body [17]. Withdrawal of nicotine as in quitting of cigarette smoking can result in intense cravings for nicotine, irritability, depression, insomnia, hunger, and difficulty concentrating [18]. The increased appetite associated with nicotine withdrawal could be due to reactivation of pathways that were previously blocked by nicotine [19]. Studies suggest that the nicotine withdrawal symptoms could result from the brain having no opposing force (dopamine) to dampen its effects. It is the lack of this opposing force that causes withdrawal symptoms [20].

The aim of the present study was to investigate the effects of nicotine exposure and discontinuation on serum insulin, glucose and glycated haemoglobin of high-fat diet fed waster rats.

Materials and Methods

This study was carried out in the department of Human Physiology, Faculty of Basic Medical Sciences, University of Port Harcourt with ethical approval number: UPH/CEREMAD/REC/MM68/053. The experiment involved 48 male wistar rats separated into 4 groups of 8 rats each which were acclimatized for a period of two weeks being provided with standard animal chow and water ad libitum. After acclimatization, all the animals were placed on high-fat diet (Margarine; blue band) in addition to the different doses of nicotine in the experimental groups. Group 1 served as control and received distilled water, Groups 2, 3 and 4 received 200µg/kg, 400µg/kg and 800µg/kg of nicotine oral solution respectively. The experiment was performed in two phases. In the first phase, the experimental groups were placed on their respective doses of nicotine solution for 4 weeks. Thereafter, 4 animals in each group were sacrificed and blood samples collected to determine their nicotine exposure plasma levels of glucose, insulin and glycated hemoglobin. In the second phase of the experiment, nicotine was discontinued in the experimental groups. The remaining 4 animals in each group continued without nicotine for another four weeks after which they were sacrificed and blood samples collected to determine their nicotine withdrawal plasma levels of glucose, insulin and glycated hemoglobin. All the parameters were determined using standard methods and values recorded.

Data were analyzed using SPSS vs 23 and presented in Tables and graphs. Continuous variables were expressed as mean ± SEM. The differences between each group were analyzed using paired sample t-test and ANOVA. Values of $p< 0.05$ were considered significant with a confidence level of 95%.

Results and Discussion

Table 1: Effect of Nicotine Exposure on Plasma Glucose, Insulin, and Glycated Hemoglobin of Waster Rats

Groups	Glucose (mmol/l)	Insulin (IU/l)	HbA1c (%)
Control	7.78±0.14	10.70±0.77	6.50±0.08
200µg/kg of nct	6.63±0.49*	14.90±1.07*	5.75±0.32*
400µg/kg nct	5.35±0.34*	18.88±0.28*	4.95±0.22*
800µg/kg of nct	4.73±0.19*	15.88±0.45*	4.55±0.13*

Values are mean ±standard error of mean

***Significant Compared to Control.**
nct; nicotine.

There was dose-dependent reduction in plasma glucose and glycosylated hemoglobin levels following exposure to nicotine. Whereas the plasma insulin levels increased significantly compared to control in high-fat diet fed wistar rats.

Table 2: Withdrawal Effects of Nicotine on Plasma Glucose, Insulin and Glycated Hemoglobin.

Groups	Glucose (mmol/l)	Insulin (IU/l)	HbA1c (%)
Control	6.95±0.18	16.30±0.35	5.98±0.11
200µg/kg of nct	5.68±0.41*	17.80±2.46	5.18±0.26*
400µg/kg nct	6.90±0.11	21.15±1.57*	6.20±0.24
800µg/kg of nct	7.35±0.27	22.75±0.93*	6.28±0.17

Values are mean ±standard error of mean

***Significant Compared to Control.**
nct; nicotine.

There was significant reduction in plasma glucose and glycosylated hemoglobin with the lowest dose of nicotine following withdrawal but no significant effect with the higher doses. Whereas the plasma insulin levels increased significantly with the higher doses following nicotine withdrawal in high-fat diet fed wistar rats.

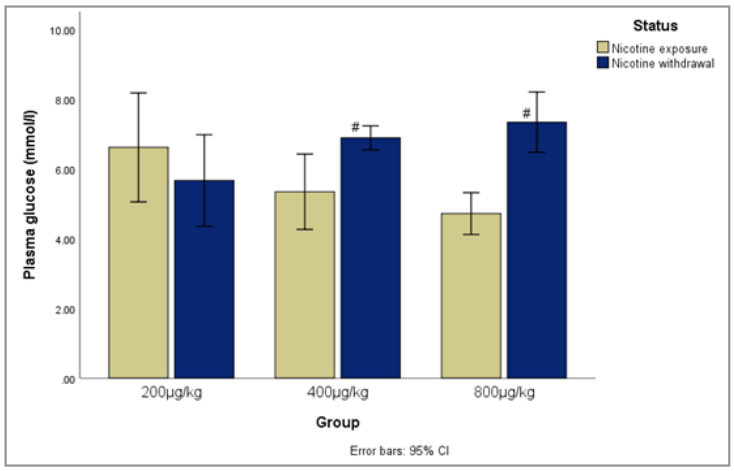

Figure 1: Plasma Glucose Levels in The Nicotine Exposure and Withdrawal Groups

The symbol, # represents significant difference in plasma glucose between nicotine exposure and nicotine withdrawal.

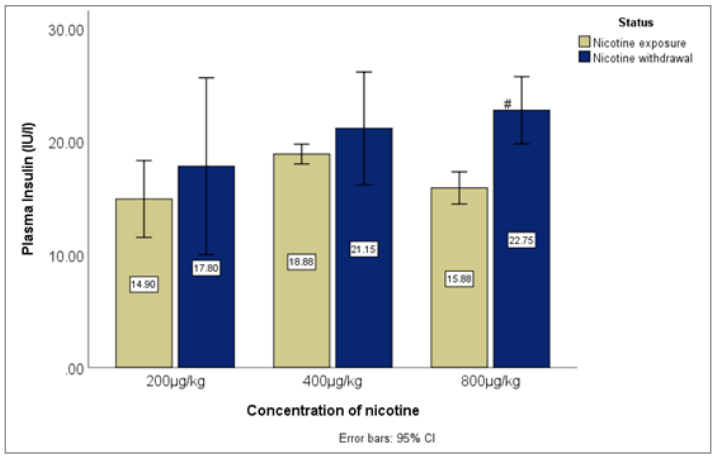

Figure 2: Comparing Plasma Insulin Levels in The Nicotine Exposed and Withdrawal Groups

The symbol, # represents significant difference in plasma insulin between nicotine exposure and nicotine withdrawal

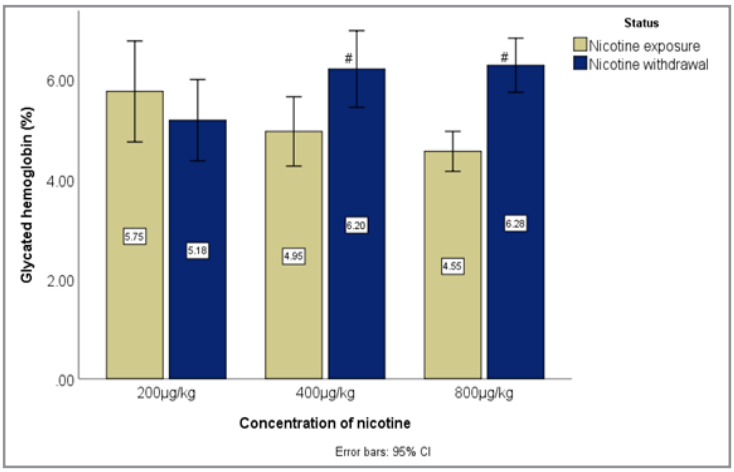

Figure 3: Comparing Plasma Glycated Hemoglobin Levels in The Nicotine Exposed and Withdrawal Groups

The symbol, # represents significant difference in plasma glycated hemoglobin levels between nicotine exposure and nicotine withdrawal groups.

Discussion

Nicotine which is commonly used as a recreational drug is known to possess highly addictive properties. The present study examined the effect of nicotine exposure on the glycemia of high fat-diet fed wistar rats. The results showed that exposure to the three concentrations of nicotine (200, 400 and 800µg/kg respectively) significantly caused a rise in plasma insulin levels but reduction in both plasma glucose and glycated haemoglobin levels compared to their control group. Physiologically, insulin is known to drive glucose into the cells and therefore has an inverse relationship with plasma glucose [21]. The reduction in both the plasma glucose and glycated haemoglobin were in a dose-dependent fashion. Previous studies have linked continues exposure to nicotine with increases in basal metabolic rate, thermogenesis and physical activity but reduction in food intake [22-24]. Most of the stimulants of the central nervous system are often used as ergogenic aids which increases energy utilization in endurance exercises [25]. However, studies suggest that nicotine as a CNS stimulant can only perform this role in lower doses [26, 27]. The possible reduction in food consumption and increased physical activity together with the increased levels of insulin in the plasma could contribute to the lowered plasma glucose shown in this study. The reduction in the levels of glycated haemoglobin following exposure to nicotine may be potentially beneficial in diabetic management. This is because a reduction or control of glycated haemoglobin is an important marker in delaying or preventing diabetic complications [28-31].

Nicotine cessation can occur when a smoker quits for some reasons. This sudden withdrawal may have many consequences including restlessness, anxiety and increase in appetite. In the present study, we examined the plasma levels of insulin, glucose and glycated haemoglobin four weeks following cessation of nicotine in wistar rats. The result showed that four weeks after cessation or withdrawal of initial 200µg/kg nicotine there were no significant changes in the levels of plasma glucose, insulin and glycated haemoglobin compared to the nicotine exposed groups. However, withdrawal, after initial exposure to 400µg/kg of nicotine was associated with significant rise in both the plasma glucose and glycated haemoglobin but no significant change in insulin compared to their respective nicotine exposed groups. Cessation, after initial exposure to high dose of nicotine (800µg/kg) resulted in significant rise in plasma levels of glucose, glycated haemoglobin and insulin compared to their nicotine exposed group. Therefore, reversal of plasma glucose and glycated haemoglobin levels could be achieved four weeks after cessation of 800µg/kg of nicotine. This result could suggest a possible association of nicotine cessation with decreased insulin sensitivity and increased insulin resistance [32].

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