Effects of Combined Administration of Nicotine and Caffeine on Adult Rat Prostate

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ABSTRACT

Objectives: Nicotine and caffeine have been shown to be a reproductive toxicant in animals and are associated with risk of cancer. The objective of this study was to evaluate the combined effect of these two drugs on rat prostate histology and serum testosterone level.

Settings: King Fahad Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia.

Design: Experimental study, animals were injected with 100 mg/kg bw of caffeine by intra peritoneal injection daily for one month, concomitantly nicotine was injected at 10mg/kg bw three times /week by subcutaneous injection. Effect on rats’ body weight, histological changes in the prostate, and on serum testosterone level were observed.

Results: Nicotine at the tested dose causes increased interacinar space with reduction in stromal tissue (loose stroma), and also many congested blood vessels were noted in the stroma. The acini themselves become dilated and thin-walled with poorly infolded mucosa and reduction in the height of epithelial lining with flattened columnar cells. An increase in testosterone level was also noted with both the group treated with caffeine alone and with the group treated with both drugs with no significant effect on alanine transaminase or cholesterol.

Conclusion: At the used dose, nicotine caused toxic effects in male rat prostate that can be antagonized by concomitant treatment with caffeine.

Keywords
Nicotine, Caffeine, Prostate, Testosterone.
INTRODUCTION

Nicotine and caffeine are considered two of the most common pharmacologically active substances used by humans and they are widely consumed substances in today’s society. Further, these substances have been on the prohibited list of World Anti-Doping Agency (WADA). The reason is their potential performance-altering effect and misuse. Unfortunately, studies investigating the influence of combined toxicity of nicotine and caffeine are few; examples of these studies are Nash et al. and Gilani et al., in which the combined effects of caffeine and nicotine on early chick embryos were investigated.

Caffeine (1,3,7-trimethylxanthine) is a member of the methylxanthine family of drugs, and it is the most widely consumed behavioral or psychoactive substance in the western world. Historically, caffeine has been subjected to extensive research worldwide to determine its impact on human health. Based on many studies, it is well established that caffeine has a psychoactive effect and that it also adversely affects the endocrine, reproductive, cardiovascular, respiratory, renal and gastrointestinal systems.

Caffeine is absorbed rapidly and completely from the gastrointestinal tract: peak plasma concentration is reached within 15-60 minutes after intake. First pass metabolism occurs as oral materials are absorbed through the small intestine into the portal circulation, in which initial metabolism by CYP450 enzyme occurs in the bowel wall and liver before entering the general circulation. Because of this first pass effect of caffeine, once it is absorbed it readily enters all body tissue. The primary metabolites for caffeine are paraxanthine, theobromine and theophylline which are detectable in all body fluids. In humans, the half-life of caffeine ranges from 2-4.5 hours.

Caffeine is metabolized in the liver, by CYP 450, mainly by cytochrome P450 1A2. Only 0.5% to 2% of ingested caffeine is excreted as such in the urine. Theobromine constitutes the largest percentage of biologically active caffeine metabolites. Its clinical effects include diuresis, cardiovascular system stimulation and increased glandular secretion. It has a longer half-life ranging from 7.2-11.5 hours.

The two main factors affecting caffeine metabolism are pregnancy and cigarette smoking. Pregnancy slows caffeine metabolism while cigarette smoking accelerates it. Cigarette smoking nearly doubles the metabolic rate of caffeine because of its high content of polycyclic aromatic hydrocarbons, which is known to increase liver enzyme activities. Its mechanism of action is as follows:

1. Antagonism of adenosine; it blocks adenosine receptors
2. Increase fatty acids oxidation
3. Increase post-exercise muscle glycogen accumulation
4. Caffeine acts as a non-selective competitive inhibitor of the phosphodiesterase bond
5. Mobilization of intracellular calcium

Nicotine is mainly obtained from the tobacco plants, which belong to the family Nicotiana tabacum. Nicotine is both a naturally occurring alkaloid and an amine composed of pyridine and pyrolidine rings.

Nicotine can be absorbed orally as well as through the skin, lungs, and gastrointestinal tract. It has a half-life of approximately 2 hours. Once absorbed it is extensively metabolized by the liver into a number of major and minor metabolites.

Nicotine has many diverse effects on humans and its metabolism is complex, involving two main pathways: Phase I and Phase II.

**Phase I:** involves microsomal oxidation of nicotine, and the most important enzyme leading to Cotinine formation is CYP2A6. CYP2A6 causes C-oxidation of nicotine leading to cotinine formation.

**Phase II:** glucuronide conjugation for nicotine and its metabolites by UDP-glucuronosyltransferase (UGT) enzyme, to produce more water-soluble compounds.

The prostate is the largest male accessory gland; it is located between the bladder neck and urogenital diaphragm, posterior to symphysis pubis. The prostate gland is composed of, base, apex, anterior, posterior and two infero-lateral surfaces. Its base is related to the neck of the bladder and its apex rests on the superior surface of urogenital diaphragm.

The studies that investigate the toxic effect of both nicotine and caffeine are few; therefore the present study was designed aiming at evaluating the effects of concomitant injection of nicotine and caffeine on the prostate histology and serum testosterone level.

MATERIALS AND METHODS

**Materials**

**General Materials**

Caffeine anhydrous pure (99%) was purchased from Scharlau Chemie S.A. Sentmenat (Barcelona), Spain and nicotine hydrogen tartrate (95%) was purchased from Sigma-Aldrich (Sigma-Aldrich Co. LLC, St. Louis, MO USA). Testosterone kit (rat) was purchased from ALPCO Diagnostics (American Laboratory Products Company, Salem, NH USA). Alanine transaminase (ALT) and cholesterol kits were obtained from Abnova Corporation (UK) (Abnova Corp, Taipei, Taiwan). All other chemicals and materials were purchased from Analar® (BHD Chemicals Ltd., Poole, England) and were of molecular biology grade.
Methods

Animals and Husbandry

Wistar rats were purchased from King Fahad Medical Research Center, King Abdullah University in Jeddah, Saudi Arabia, and were housed six per polycarbonate cage with wood shavings as bedding. Animals were maintained under a controlled environment at 22 ± 2°C and relative humidity of 40–65% with 12 h/12 h light dark cycles throughout the experimental period. The rats were fed laboratory chow. Tap water in plastic bottles with steel sipper tubes were used for an ad libitum supply of water.

Study Designs

Single animal study was undertaken during the work described herein, examining different aspects of nicotine and caffeine toxicity in male rats. Full details of the study protocol are provided below:

Characterization of Nicotine and Caffeine Mediated Prostate Toxicity

I - Animals and Dosage Formulation

A total of 24 virgin male Wistar rats were used and allowed to acclimatize at the experimental environment for 4 days before initiation of dosing. The rats were 60 days old and weighed 200-250 gm. The doses of nicotine and caffeine used were 10 and 100 mg/kg bw/day respectively, for 30 consecutive days. This is the dose range for nicotine which has previously been reported in the literature to produce adverse effects on the male reproductive system[20]. For the caffeine, the choice of this dose is dependent on the protective results of the biochemical study conducted by Lee et al.[21]. Dosing solutions for both chemicals were freshly prepared daily using 9% normal saline, and were based on the initial body weights of the rats at day zero. The dissolved caffeine was filtered through a disposable sterile filter membrane immediately before injection. The control group was injected with 1 ml of 0.9% normal saline subcutaneously 3 times/week and also were injected intraperitoneally daily with normal saline.

II - Experimental Scheme

The major aim of the study was to induce the toxic effect of nicotine and caffeine, by using high doses of previously mentioned substances to induce prostatic damage. The study was conducted with 3 different treatment groups and one vehicle control group with 6 randomly chosen animals in each group (n = 6). Animals were dosed with Nicotine 3 times per week for 4 weeks by subcutaneous (SC) injection and were dosed with Caffeine daily for 4 weeks by intraperitoneal injection (IP). Twenty-four hours after the last dose, 3 ml of blood was collected from retro-orbital sinus in plain tubes, and then the rats were killed by cervical dislocation under ether anesthesia. Blood samples were centrifuged at 2000 g for 10 minutes and clear serum was separated from the clot and stored at -80°C for further work. The prostates of all animals were isolated for further experimental evaluation.

Summary of the rats groups is as follows:
G-1: Control
G-2: Nicotine Alone
G-3: Caffeine Alone
G-4: Nicotine + Caffeine

III - Experimental Methods

Histopathological Evaluation

Prostate of all rats were fixed by formaldehyde fixation (10% natural buffered formalin). Organs were initially fixed for 24 h in formalin and then removed for preliminary cutting, and tissues were further fixed for another 24 h in 10% neutral buffered formalin. This method of fixation was according to Kagami et al.[23].

Processing of Fixed Sections

Following fixation of tissues by previous methodology, tissues were then processed using standard laboratory procedures for histology. Tissues were briefly embedded in paraffin blocks, sectioned perpendicular to the longest axis of the testis at approximately 3-5μm thickness and stained with Hematoxylin and Eosin stain (H&E stain) and Periodic Acid Schiff stain (PAS stain). Stained sections were mounted with dextran-plasticizer xylene (DPX) and were examined using light microscopy (Olympus BX51TF) at the indicated magnifications and representative images photographed with an Olympus DP 72 camera.

Light Microscopy

Slides were examined for histological changes using an Olympus BX51TF, light microscopy at ×4, × 20, × 40 magnification.

ELISA Assay

Testosterone Assay

Direct quantitative determination of free testosterone in rat serum was performed by using an ELISA kit for competitive enzyme immunoassay. All reagents were prepared/or reconstituted according to the product protocol. The mean absorbance for each standard was calculated and calibration curve plotted on semi-log paper with the mean optical density on the Y-axis and the calibrator concentrations on the X-axis and the values of the unknown samples were read directly from the curve.

Statistical Analysis

Differences between obtained values (mean ± SEM) were compared by one-way analysis of variance (ANOVA), using SPSS 20 program followed by Bonferroni multiple comparison test. A P-value less than 0.05 was used as the criterion for a statistically significant difference.

Ethical Committee Approval

The research was approved by the Biomedical Ethics Research Committee, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.
RESULTS

Effect of Nicotine and Caffeine on Rats Body Weights

Administration of nicotine and caffeine to rats at doses of 10 mg/kg and 100 mg/kg/day respectively for one month, did not show any significant difference in rats’ body weight during the treatment period (P < 0.05) in comparison to the control group.

Also no significant body weight changes were detected at the end of the experiment in comparison to the control group.

Effect of Nicotine and Caffeine on Serum Testosterone Level

As testosterone is produced within the Leydig cells of the testis, we next examined the impact of Nicotine- and caffeine-mediated toxicity on circulating testosterone levels. There was a very significant increase (P < 0.001) with 1 ± SEM in blood testosterone level detected in rats treated with Caffeine alone (100 mg/kg) and in the group treated with Nicotine and Caffeine together, when compared to the normal control group, with no statistically significant difference detected between Nicotine treated rats when compared to the control group (Fig. 1).

Effect of Nicotine and Caffeine on Serum ALT and Cholesterol Level

No significant difference was detected among all groups regarding the cholesterol and ALT serum levels when compared to the control group (P < 0.05). The different means for all groups are shown in Table 1.

Histopathology

Some evidences of histological changes in the prostate were observed in rats treated with nicotine and caffeine when compared with the control rats. In control rats (as shown in Fig. 2) prostatic acini appeared normal with different normal general cellular arrangement with apparent luminal acidophilic secretions, and normal appearance of infolded mucosa of the acini. Also, the prostatic acini are separated by narrow intercellular spaces occupied by minimal stroma (Fig. 2A).

However, rats injected with 100 mg/kg bw caffeine for one month (Fig. 2B), appeared to have stimulatory effect on prostate, which showed some histological changes in the prostate including: increased number of prostatic acini with increased mucosal infoldings, compared to the control, with no major effect on stromal connective tissue components apart from reduction in spaces between acini. In addition reduction in the height of epithelial lining of some acini with flattened columnar epithelium with empty lumen was detected. The prostatic secretions appeared normal in most of the sections when compared to the control.

Surprisingly, rats treated with nicotine alone had the opposite effect to caffeine on histological features of the prostate. As shown in Figure. 2C, 2D nicotine injection over one month caused clear damage to the prostate in the form of increased interacinar space with a reduction in stromal tissue (loose stroma, and also many congested blood vessels were noted in the stroma. The acini

| Mean ALT Level (U/L) | Mean Cholesterol Level (mg/dl) | No. of Cases | Rat Groups   |
|---------------------|--------------------------------|--------------|--------------|
| 53.00 ± 0.66        | 66.33 ± 0.33                   | 6            | Control      |
| 59.17 ± 0.33        | 55.50 ±1.00                    | 6            | Nicotine     |
| 50.83 ± 0.50        | 69.67 ± 0.66                   | 6            | Caffeine     |
| 64.20 ± 1.00        | 63.83 ± 0.50                   | 6            | Nicotine + Caffeine |
| 56.48 ± 0.23        | 63.83 ± 0.23                   | 24           | Total        |

**TABLE 1.**
Means of cholesterol and ALT level in serum of all rat groups. No significant difference was detected between the groups (P < 0.05)
FIGURE 2.

(A) Light microscopy of transverse sections of prostate isolated from control adult Wistar rat showed prostatic acini, note also the closely packed prostatic acini of different sizes and infolded mucosa (arrows), these acini are separated by narrow interacinar spaces occupied by minimal stroma, 10 x magnification; (B) and prostate isolated from caffeine-treated Wistar rats, showed increased mucosal infoldings (arrow) in the acini after caffeine treatment, with increased secretory activity of glands. Caffeine was given by IP injection (100 mg/kgbw / daily for one month) 10x magnification; (C) prostate isolated from Nicotine-treated rats. Nicotine was given 3 times/week by (SC) injection for one month, showed increased interacinar space (black strike) with a reduction in stroma and decreased mucosal infoldings. 20x magnification; (D) Prostate isolated from Nicotine-treated rats. Showed dilated thin-walled prostatic acini, with poorly infolded mucosa (arrows) with an irregularity in epithelium indicating a degenerated basement membrane, also note a reduction in the height of epithelial lining with flattened columnar cells, 20 x magnification. Sections were stained with H&E stain and viewed with light microscopy.
themselves became dilated and thin-walled with poorly infolded mucosa and a reduction in the height of epithelial lining with flattened columnar cells.

Finally, in the group of rats treated with both nicotine and caffeine, they showed both equal effects of these drugs in the prostate (Fig. 3). While caffeine causes an increase in mucosal folding and an increase in acini number, nicotine causes massive destruction for the stroma with apparent reduction in stromal tissue with widening a of interacinous spaces of the prostate gland, and also a reduction in secretory activity of the acini. In addition, a flattening of epithelium lining of some acini was noted.

**DISCUSSION**

The present study investigated the effects of concomitant injection of nicotine and caffeine on prostate histological structure, body weights and serum testosterone level in adult male rats.

The results of this study indicate that both nicotine and caffeine have toxic effects on prostate histology compared with the normal control. Caffeine is mostly stimulant to the prostate. However nicotine is inhibitory, so they are antagonizing each other. There are many studies indicating toxic effects of cigarette smoking on the male reproductive system\[22,23\]. However, articles investigating the toxic effects of caffeine on the prostate are sparse in the literature.

**Effects of Concomitant Injection of Nicotine and Caffeine on Rats’ Body Weights**

This study showed that the concomitant administration of nicotine (daily) and caffeine (3 times a week) at doses of 10 and 100 mg/kg bw/day, respectively, for one month has no significant effect on rat’s body weight when compared to the control. Also no significant effect on body weight change was noted. Many other studies conducted on nicotine alone revealed a significant decrease in body weight gain and food intake in experimental rats\[24\] after administration of nicotine. These results were also demonstrated by Ahmadnia et al.\[25\]. So in this study, extending the time of exposure to drugs for more than one month might have some significant effect on rats’ body weights.

**Effects of Concomitant Injection of Nicotine and Caffeine on Histological Structure of the Prostate and on Testosterone Level**

In this study nicotine administration over one month showed a damaging effect on the histological structure of the prostate in the form of a widening of interacinous space with a thinning of the stroma, in addition to a widening and thinning of the acini wall with a decrease in normal mucosal infoldings. Also, it decreased the height of columnar lining epithelium of the acini, with atrophy in the basement membrane and it also affected the secretory activity of the acini, by decreasing their secretions.

Further, in this study caffeine administration over one month showed an effect opposite to nicotine, in the form of an increased number of acini, mainly of small size, with an increase in mucosal infoldings and epithelial height of the acini, and reduced the space of the stroma between the acini with increased secretory activity. Surprisingly, for rats treated concomitantly with both drugs the prostate showed both a stimulatory effect of caffeine in some fields in the sections and other fields showed an inhibitory effect of nicotine. This study showed also a significant increase in serum testosterone level compared to the control in the group of rats treated with caffeine alone and in the group of rats treated with concomitant injection of nicotine and caffeine for one month. However, no significant difference...
in testosterone level was detected in the group of rats treated with nicotine alone when compared to the control.

The explanation for these contradictory effects of nicotine and caffeine on the histological structure of the prostate is mainly related to hormonal changes that resulted from this exposure. One study conducted by Pesta et al.[13] on studying the effect of nicotine on reproductive hormones in adult male mice showed a significant (p < 0.05) decrease in testosterone level in adult male mice treated with nicotine alone, and this result is contradictory to these results. However, it is reported that the effect of nicotine on testosterone level in experimental animals is largely contradictory among various studies[15]. Regarding caffeine a few studies have investigated the association between male caffeine consumption and testosterone consumption in adult life and level and some are conflicting. A single study reported by Pasqualotto et al.[26] serum level showed a significant high testosterone concentration was associated with a high caffeine intake in human males, and this result supports this study's results regarding testosterone level in caffeine treated rats. Further, another study conducted by Audi et al.[27] studying the association between cigarette smoking and the effect on serum level of testosterone in male rats indicated that serum testosterone level was decreased in cigarette smoking animals compared with control rats. It is known that the prostate and many other male glands are under hormonal control. Hence, any drug (e.g., caffeine) that can increase the male hormone level (e.g., testosterone) will increase the activity of the gland, and any drug (e.g., nicotine) that can decrease this hormone will decrease the activity of this gland; beside nicotine's inhibitory effect on pituitary hormones such as LH and FSH[28].

However the concomitant effect of both nicotine and caffeine on male rat prostate in this experiment cannot yet be explained! Both effects of the two drugs can be seen in the same section and this needs further investigation.

CONCLUSION

In conclusion, these findings show that nicotine and caffeine injection over one month results in histological changes in rat prostate, with nicotine being more inhibitory while caffeine is more stimulatory. Also noted was an increased testosterone serum level in the caffeine injected group and the group with concomitant injection of both nicotine and caffeine. In modern life, caffeine and nicotine are the most widely consumed substances worldwide. Therefore the authors advise men who are consuming these two substances mostly at the same time to make periodic investigations for their hormonal levels, in particular to testosterone and try to decrease the daily intake of these substances as much as possible in order to protect their reproductive organs, particularly the prostate.

RECOMMENDATION

Further investigations are needed to explain the biochemical basics of the action of these two prohibited substances

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التأثير السمي لمادة النيكيوتين والكافيين معا على غدة البروستاتا لدى الجرذان

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المستخلص.

المقدمة ومشكلة الدراسة: من المعروف بأن مادة النيكيوتين ومادة الكافيين لهما تأثير سمي على الجهاز التناسلي الذكري للجرذ، وهو متوقع أيضا بحدوث سرطانات في العديد من الدراسات المخبرية وتهدف هذه الدراسة إلى اختبار تأثير النيكيوتين والكافيين معا في وقت واحد على غدة البروستاتا للجرذ.

المنهج المتبوع للدراسة: تم حرق الجرذان بمادة النيكيوتين بجرعة مقدارها 10 مل لكل كجم للجرذ لمدة شهر بمعتدل ثلاث مرات في الأسبوع داخل الصفيق، متناسمين مع حرقهم أيضا بمادة الكافيين بجرعة مقدارها 100 مل لكل كجم من الوزن للجرذ لمدة شهر ثلاث مرات في الأسبوع تحت الجلد، وبعد انتهاء هذه الحقن تم أخذ عينات من الدم واستئصال غدة البروستاتا لجميع الجرذان.

ملخص النتائج: بعد صبغ الأنسجة بصبغة هيماتوكسيلين تأكد وجود تأثير لمادة النيكيوتين على البروستاتا وذلك بانسخ الفوجه النسيجي بين خلايا البروستاتا مع قلة النسيج الضام فيها، مع اتساع الخلايا الغدية ذاتها بشكل غير منتظم مع زيادة ملحوظة في هرمون التستوستيرون في المجموعات التي حققت بالدواء معا.

الخلاصة وأهم النتائج: تسبب الجرعة المستخدمة من دواء النيكيوتين سمية نسيجية واضحة على غدة البروستاتا للجرذان ويمكن عكس تأثيرها بحق الكافيين.