



Article

Physiological Study Of The Effect Of Codeine Addiction By Dosing Different Concentrations On Testosterone Levels In Male Albino Rats

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Received: April 11, 2025

Revised: April 29, 2025

Accepted: July 2, 2025

Published: July 11, 2025



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Abstract: This study aimed to evaluate the effect of codeine on testosterone levels in male albino rats. Thirty male rats were divided into three groups: a control group (which did not receive codeine) and two experimental groups (which received different doses of codeine). The doses were administered daily for 8 weeks, and blood testosterone levels were measured using ELISA. The results showed a significant decrease in testosterone levels in the groups receiving codeine, with a greater decrease in the group receiving the high dose. These results suggest that codeine may negatively affect hormonal function in males, calling for further studies to understand the exact mechanism of this effect.

Keywords: codeine , testosterone , FSH , LH .

INTRODUCTION

ult of this inhibition, which lowers the activity of neurons that convey pain signals. Furthermore, codeine reduces the cough reflex by affecting the cough center in the medulla oblongata (Karch, 2015).

Codeine is well absorbed orally, with peak plasma concentrations occurring within 1–2 hours of administration. It is primarily metabolized in the liver via the CYP2D6 enzyme to morphine, the pharmacologically active form. Some of it is also converted to inactive compounds that are excreted by the kidneys. The effect of codeine depends on the activity of the CYP2D6 enzyme, with genetic differences between individuals affecting the drug's efficacy (Zanger & Schwab, 2013).

Because of its opioid effects, codeine is a substance of abuse. In addition to increasing the danger of overdosing, which can result in respiratory depression and even death, non-medical use can induce dependence and addiction. Because of its potential for addiction,

codeine is categorized as a restricted substance in many countries (Manchikanti et al., 2010).

High dosages or extended use of codeine, however, can have a number of negative consequences, including those on the endocrine system, particularly on levels of sex hormones like testosterone. The main male hormone, testosterone, is essential for preserving male sexual traits, promoting sexual function, and preserving bone density and muscle mass. Male testicles are the primary site of testosterone production, and the hypothalamic-pituitary-gonadal axis controls this hormone.

Low testosterone levels can have a detrimental effect on general health and sexual function if this axis is disturbed. Recent research has indicated that the use of opiates, such as codeine, may have a detrimental impact on male testosterone levels. Due to their physiological similarities to humans in many ways, including how the endocrine system reacts to opioids, albino rats have been used as an animal model to examine these effects. (Smith and others, 2020).

With a ketone group at position three and a hydroxyl group at position seventeen, testosterone is a member of the androstenediole steroid family. It is produced by a sequence of chemical events that begin with cholesterol and end with inactive metabolites in the liver. The androgen receptor is bound by testosterone, which then activates it.

The Leydig cells of the testes in males secrete testosterone in large quantities, whereas the female ovaries produce it in smaller amounts. Adult male testosterone levels are roughly seven to eight times higher than those of adult female testosterone levels. Males produce about 20 times as much testosterone per day as females do due to their higher metabolic rate, which makes females more susceptible to the hormone's effects (Mooradian et al., 1987).

During puberty, testosterone production starts to rise sharply, peaks in the 30s, and then starts to progressively fall after that. Testosterone is essential for the generation of sperm and is strongly associated with libido. This hormone also has an impact on bone and muscle mass as well as body fat distribution.

And red blood cell production. Testosterone levels can also affect mood in men (Luetjens & Weinbauer, 2012).

The Leydig cells of the male testes and the female ovaries are the main sites for testosterone production. In both sexes, it can also be produced in the adrenal cortex (Burger, 2002; Dohle et al., 2003). Furthermore, research has demonstrated that the manufacture of steroids, including testosterone, involves a complex mechanism of action because of its steroidal composition and the variety of metabolic pathways.

According to the traditional process, testosterone triggers or inhibits gene expression by binding to androgen receptors in the cytoplasm before traveling to the nucleus and attaching to hormone response elements on DNA (Tsai & O'Malley, 1994). Testosterone can activate membrane receptors or a number of second messengers inside the cell, according to new discoveries of non-genomic pathways (Michels & Hoppe, 2008).

Depending on the enzymatic processing of the cells, the enzymes aromatase and reductase can convert testosterone to either dihydrotestosterone or estradiol. Gonadotropin-releasing hormone (GnRH), which is released by the brain to activate the gland, is the primary regulator of sex hormone synthesis.

LH boosts the synthesis of testosterone by increasing the expression of the StAR protein in target cells (Ubuka et al., 2014).

Adults have pulsating GnRH secretion that peaks when they sleep, which causes testosterone levels to rise in the early morning (Lord et al., 2014). Leydig cell regression and the slowing of GnRH production cause testosterone levels to progressively decrease with age. Males in their sixth decade of life have a sharp drop in testosterone levels (Basaria, 2013).

The significance of the research:

The main male sex hormone, testosterone, is essential for mood, bone density, muscle mass, and sexual health. Any drop in testosterone levels can result in psychological side effects including anxiety and sadness as well as sexual problems like erectile dysfunction,

poor libido, and infertility (Johnson & Williams, 2019). Thus, it is crucial to comprehend how drugs like codeine affect testosterone levels.

The purpose of the study

This study sought to ascertain whether the effects of varying dosages of codeine on male albino rats' body weight and testosterone levels were dose dependant.

Materials and Methods :

Experiment design :

Three groups of 20 male rats each were randomly selected from 60 white male rats that were 8–10 weeks old:

The control group was left untreated.

Group 1 in the experiment was given a small dosage of codeine (10 mg/kg each day).

Group 2 in the experiment was given a high dosage of codeine (30 mg/kg each day).

Administration of Codeine :

For 8 weeks, codeine was given orally daily. To make sure there were no severe adverse effects, the rats were observed every day.

Measurement of Testosterone Hormone :

According the manufacturer's directions, blood samples were taken from each rat at the conclusion of the experiment, and ELISA technology was used to measure the testosterone levels.

Statistical Analysis :

ANOVA test was used to compare the results between groups, and a p value < 0.05 was considered statistically significant.

Results :

Morphological changes in rats :

Because many of the rats that were exposed to doses of codeine at concentrations (10 mg/kg and 30 mg/kg) showed signs of sluggish clearance and general weakness in the physical structure, in addition to noticeable hair loss. In contrast, none of these symptoms were observed in the control group that did not receive any doses of codeine

Body weight changes

The results of the statistical analysis of this study revealed a statistically significant decrease (P < 0.05) in the average body weight of the group of rats that were given daily oral doses of codeine at concentrations (10 mg/kg and 30 mg/kg) for 8 weeks, compared to the control group.

Table (1) Study the effect of different concentrations of codeine (10, 30 mg/kg) on the average body weight of male albino rats dosed orally for 80 days compared to the control group.

Group		Body weight/gm (mean ± standard error)
Control group		392.5 ± 29.8
Low dose 10 mg/kg		240.1 ± 27.5

High dose 30 mg/kg	224.7 ± 15.2
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ANOVA test showed a significant difference between groups ($p < 0.001$).

3.3. Testosterone levels :

The results showed a significant decrease in testosterone levels in the groups receiving codeine compared to the control group. The percentage of decrease was higher in the group receiving a high dose of codeine.

Table (2) Study the effect of different concentrations of codeine (10, 30 mg/kg) on the testosterone level in male albino rats dosed orally for 80 days compared to the control group.

Group	Average Testosterone Level (ng/mL)
Control group	0.3 ± 5.2
Low dose 10 mg/kg	0.4 ± 3.8
High dose 30 mg/kg	0.2 ± 2.1

ANOVA test showed a significant difference between groups ($p < 0.001$).

DISCUSSION

Changes In Body Weight

Scientific studies have shown that codeine use can have significant effects on body weight in male albino rats. These weight changes could be due to several factors, including metabolic effects, appetite changes, and other side effects associated with opioid use. Research suggests that codeine may affect appetite through its effects on the central nervous system, which can cause appetite suppression or increase, depending on the dose and duration of use. In a study conducted on male albino rats, rats given high doses of codeine for a long period of time showed a decrease in food intake, resulting in significant weight loss, Codeine may affect metabolic processes, leading to changes in energy use and fat storage. (Smith & Jones, 2020) .

Other scientific studies have shown that codeine addiction can negatively affect body weight, especially when used for long periods. There is a study conducted by researchers on male albino rats. The rats were given daily doses of codeine for up to 8 weeks. It was found that the rats exposed to codeine showed a significant decrease in body weight compared to the control group that did not receive the drug. The average weight loss in the codeine-treated group was approximately 15–20% of initial body weight, while the control group maintained or slightly increased their weight (Smith et al., 2018).

This weight loss can be attributed to several factors related to the physiological and psychological effects of codeine. The most important of these factors are: appetite suppression, gastrointestinal disturbances, and increased metabolic activity.

Possible causes of weight loss

1. Appetite suppression

Codeine, as an opium derivative, directly affects the central nervous system, especially the satiety and hunger centers in the hypothalamus.

When codeine binds to opioid receptors in the brain, the release of ghrelin, known as the “hunger hormone,” is inhibited, leading to a decrease in feelings of hunger. At the same time, the release of satiety hormones such as peptide YY (PYY) and leptin is stimulated, which promote feelings of fullness and reduce the desire to eat (Jones & Taylor, 2019).

In a study in male rats, rats receiving daily doses of codeine were observed to reduce their food intake by up to 30% compared to the control group. This reduction in food intake was accompanied by a gradual decrease in body weight, suggesting that appetite suppression is a major factor in codeine-associated weight loss (Smith et al., 2018).

2. Gastrointestinal disturbances

Codeine is known to have a depressant effect on the motility of the gastrointestinal tract, as it binds to opioid receptors in the intestine, which leads to slowing down the movement of the intestine and increasing the absorption of water from the colon. This effect causes chronic constipation, which is a common side effect of codeine use.

Chronic constipation can lead to malabsorption of nutrients, as the digestive system becomes less efficient at extracting vitamins, minerals, and energy from food (Brown et al., 2020).

In a study of male albino rats, rats receiving codeine showed clear signs of constipation, including decreased defecation frequency and increased stool hardness. Additionally, decreased blood levels of essential nutrients, such as glucose and protein, were observed, suggesting that gastrointestinal disturbances contributed to weight loss (Brown et al., 2020).

3. Increased metabolic activity

Some studies suggest that codeine may increase the basal metabolic rate (BMR), leading to burning more calories even at rest. This effect may be attributed to increased activity of the sympathetic nervous system, as codeine stimulates the release of hormones such as adrenaline and noradrenaline, which increase heart rate and energy expenditure (Lee et al., 2017).

The study agreed with a study conducted on male rats, which noted that rats receiving codeine showed an increase in metabolic rate by up to 20% compared to the control group. This increase in metabolic activity was accompanied by a decrease in body fat stores, which contributed to weight loss (Lee et al., 2017).

4 . 2 . Testosterone levels :

The results indicate that codeine negatively affects testosterone levels in male albino rats. This effect may be due to codeine inhibiting the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, leading to decreased secretion of luteinizing hormone (LH) from the pituitary gland, and thus decreased testosterone production from the testes (Smith et al., 2020).

These findings are consistent with previous studies that have shown that opioid analgesics such as morphine and tramadol lead to decreased testosterone levels (Johnson & Williams, 2019). For example, a study by Daniell (2002) showed that high-dose morphine use significantly decreased testosterone levels in males. In addition, another study indicated that tramadol causes a decrease in LH and testosterone levels, supporting the idea that opioid analgesics affect the hormonal axis (Rahnama et al., 2013).

A study by Al-Griw et al. (2018) also showed that codeine negatively affects male fertility, resulting in decreased sperm count and changes in testicular tissue. These findings reinforce the hypothesis that codeine may affect reproductive function in general, not just testosterone levels.

4 . 3 . Effect of opioid analgesics on the endocrine system :

Several studies suggest that opioid analgesics affect the hormonal system in general. For example, a study by Abs et al. (2000) showed that patients taking morphine for long periods of time had decreased levels of testosterone and growth hormone. In addition, another study suggested that hydrocodone caused a decrease in testosterone levels in males (Daniell, 2008).

Scientific evidence also suggests that opioid analgesics affect the hormonal system through multiple molecular mechanisms. For example, a study by Ceccarelli et al. (2006) showed that morphine inhibits GnRH secretion from the hypothalamus by activating opioid receptors in the central nervous system. In addition, another study suggested that opioid analgesics affect calcium signaling in Leydig cells in the testes, leading to decreased testosterone production (Rahimian et al., 2012).

4 . 4 . Clinical effects :

These findings suggest that chronic use of codeine may have negative effects on male sexual and reproductive health. Therefore, testosterone levels should be monitored in patients taking codeine for long periods. Additionally, A study suggests that low testosterone levels may increase the risk of osteoporosis and cardiovascular disease (Katz et al. 2013).

Conclusion :

1 . Evaluation of the effect of codeine on the pituitary-testicular axis (HPG axis): The effect of codeine on levels of specific hormones (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) is confirmed by studying the effect of codeine on levels of specific hormones (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) to understand the precise pattern of its effect on testosterone.

2 . Oxidative stress analysis: Study of the effect of codeine on oxidative stress in the testes, as evidence suggests that oxidative stress may be a major factor in damage to Leydig cells responsible for testosterone production.

3 . Study the effect of codeine on growth, as studies indicate that opioid analgesics may lead to a deficiency of this hormone.

The results of this study show that the use of high doses of codeine can cause a significant decrease in testosterone levels in male albino rats. In addition, a significant decrease in body weight was observed in the rats exposed to the drug. These results indicate the importance of conducting further research to understand the mechanisms behind these effects, and they also emphasize the need to monitor the hormonal side effects resulting from the use of opioid analgesics.

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