RESEARCH ARTICLE

Study the Effect of Some Drugs on The Serotonin Hormone and Liver Tissue in Male Rats

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ABSTRACT

Serotonin or 5-Hydroxytryptamine is a neurotransmitter that is synthesized from the transformation of the amino acid Tryptophan. It is found in plants and animals and is involved in many physiological processes, its chemical formula is $C_{10}H_{12}N_2O$, and 90% of the total serotonin in the human body can be found in the digestive system and platelets. It is synthesized in the brain's nerve cells; serotonin is an essential neurotransmitter for the human nervous system. This study was conducted to study the negative effects of tramadol, pseudoephedrine, and codeine phosphate on the serotonin hormone in adult Albino rats, as this study used 24 animals. Of the male rats, which were divided randomly into four groups, each group included 6 animals, which is the Control group that was given regular drinking water and food daily, and the group of rats treated with tramadol at a dose of 50 mg/kg of body weight for a period of 30 days, group of rats treated with pseudoephedrine at a dose of 40 mg/kg of body weight for a period of 30 days, group of rats treated with drug codeine phosphate at a dose of 10 mg/Kg of body weight for a period of 30 days, the animals were dosed with drugs by the oropharyngeal tube at a dose of 1-mL and after the end of the experiment period 30 days, the animals were starved for 12 hours and then anesthetized with chloroform, then blood samples were withdrawn from the heart Directly by the cardiac heart puncture method, 5-6 mL of blood was drawn and placed in test tubes devoid of anticoagulant, then left for 15 minutes at laboratory temperature, after which the serum was separated by a centrifuge at a speed of 3000 cycles/min for a period of 15 minutes, serum was divided in Eppendorf tubes and kept at -20°C until the examination was performed, liver samples were taken and fixed in 10% formalin until histological sections were made.

Keywords: Codeine phosphate, Liver tissue, Male rats, Serotonin, Tramadol, Pseudoephedrine.

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INTRODUCTION

Serotonin 5-Hydroxytryptamine (5-HT) is a neurotransmitter that is synthesized from the transformation of the amino acid Tryptophan; it is found in plants and animals and is involved in many physiological processes, its chemical formula is $C_{10}H_{12}N_2O$, and 90% of the total serotonin in the human body can be found in the digestive system and blood platelets, and it's synthesized in the nerve cells in the brain, serotonin is an essential neurotransmitter for the human nervous system, for behavioral and neuropsychological processes in which serotonin enters include: mood, perception, reward, anger, aggression, appetite, memory, sex, and attention, the intestinal chromaffin cells and neurons to stimulate serotonin in the intestinal muscle plexus accumulate and secrete serotonin, which acts as a regulator of the intestinal secretion, movement, and sensation.[1] Serotonin can be found in the blood platelets.[2] When a blood vessel injury occurs, blood platelets release serotonin into the blood, which acts as a constrictor of blood vessels and thus acts as a coagulant; serotonin is metabolized into 5-hydroxyindoleacetic acid mainly by liver and excreted by kidneys in its final stage. Serotonin affects a variety of physical and psychological functions and is associated with bone metabolism, breast milk production, liver regeneration and cell division, and activates the vomiting center in the brain, causing nausea and an increase in osteoporosis.[3-5]

MATERIALS AND METHODS

Experimental Animals Used in the Study

In this study, adult Albino male rats ranged of weight between (230–270) gm and their ages 10 weeks. They were prepared from the animal house of Tikrit University and placed under standard conditions. Animals were dosed with drugs by the oropharyngeal tube at a dose of 1-mL. After the end of the experiment period 30 days, the animals were starved for 12 hours and then anesthetized with chloroform. Blood samples were withdrawn from the heart Directly by the cardiac heart

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puncture method, 5-6 mL of blood was drawn and placed in test tubes devoid of anticoagulant, then left for 15 minutes at laboratory temperature, after which a centrifuge separated the serum at a speed of 3000 cycles/min for a period of 15 minutes, serum was divided in Eppendorf tubes and kept at -20°C until the examination was performed. Serotonin concentration was measured by a kit of serotonergic measuring from Sunlongbiotech, and liver samples were taken to make the histological sections, examine and imaging them.

Drugs Used in the Study

1. Tramadol with dose of 50 mg/kg of body weight[6]
2. Pseudoephedrine with a dose of 40 mg/kg of body weight[7]
3. Codeine phosphate with a dose of 10 mg/kg of body weight[6]

Experience design

In this study, 24 animals were used and divided into four groups. Each group included (6) animals, which are as follows: -

1. The first group (G1): This group was given regular drinking water and food (standard diet) daily for 30 days.
2. The second group: The group of rats treated with tramadol at a concentration of 50 mg/kg of body weight, and the drug was dosed by the oropharyngeal tube at a dose of 1-mL for 30 days.
3. The third group: The group of rats treated with pseudoephedrine at a concentration of 40 mg/kg of body weight, and the drug was dosed by the oropharyngeal tube at a dose of 1-mL for 30 days.
4. The fourth group: The group of rats treated with codeine phosphate at a concentration of 10 mg/kg of body weight, and the drug was dosed by the oropharyngeal tube at a dose of 1-mL for 30 days.

Histological Study

Tissue sections were prepared and stained with hematoxylin and eosin stain according to the method by (Bancroft & Steven, 1982).

RESULTS AND DISCUSSION

The results shown in the chart showed a significant increase in the likelihood level ($p \leq 0.05$) in the group treated with tramadol, which was (116.8 ± 14.1) when compared to the control group, which was (79.4 ± 8.54). In contrast, the group treated with pseudoephedrine did not show that was (76 ± 2.36) significant differences when compared to the control group, while the group treated with codeine phosphate showed a significant increase, as it was (102 ± 10.25) when compared to the control group.

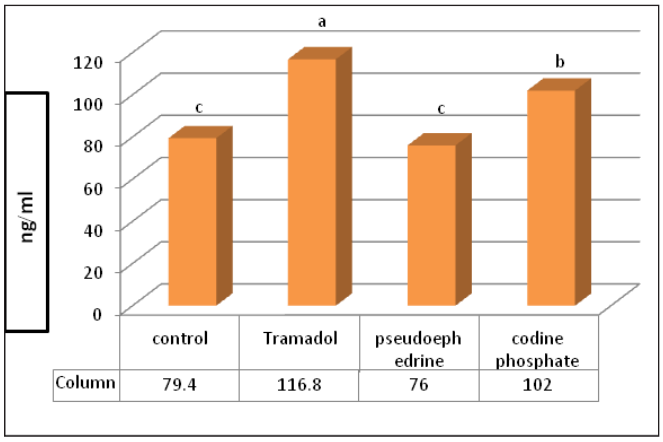
In this study, there was a significant increase in the levels of serotonin hormone concentration in the group treated with the drug tramadol compared to the control group, and this indicates an increase in the level of serotonin concentration in the blood serum resulting from the hormone exit from the nerve cells into the external cellular environment. This results from taking the drug tramadol, which leads to some cases of Serotonin Syndrome (SS), which can occur with increased intake of tramadol or tricyclic antidepressants,[8] as tramadol is a class of selective serotonin reuptake inhibitors (SSRIs).[9] This causes inhibition of serotonin's reabsorption from the synaptic cleft to the pre-synaptic cell, thus increasing its concentration in the synaptic cleft and increasing the ability to bind to the postsynaptic receptors.[10] This drug is prescribed in cases of severe depression, anxiety, sleep, and eating disorders,[11] tramadols can cause epileptic seizures as indicated.[12] Tramadol is caused by a defect in the work of the cytochrome p450 enzymes associated with the integral proteins of the inner mitochondrial membrane or the membrane of the endoplasmic reticulum, which metabolize basic substances and play an important role in metabolism. In the liver mainly,[13] an increase in serotonin concentration in some extreme cases may cause toxicity, and the analgesic effect is due to it by working to block the absorption of serotonin and norepinephrine in the spinal cord region.[14] Excessive may lead to severe serotonin syndrome, which in some cases can be fatal.[11,15]

As for the group treated with the drug pseudoephedrine, it did not show a significant difference in the level of serotonin concentration compared with the control group, which may be due to the reason that pseudoephedrine has a direct effect on the level of the hormone serotonin when used for a limited period. Pseudoephedrine is one of the amines that act indirectly on the receptors of the neurotransmitters. On the alpha and beta receptors (a1 and b1) found in postsynaptic cells.[16]

The group treated with the drug codeine phosphate showed a significant increase when compared to the control group, possibly due to the opioid effect of codeine, as codeine is metabolized in the liver to morphine by removing the methyl group, and the products of codeine metabolism, especially morphine, activate the μ-opioid receptor[17] codeine is also metabolized to codeine-6-glucuronide (C6G), which upon reaching high levels in the blood prevents more codeine from being converted into morphine and has a major role in causing physical habituation to codeine, as is CYP2D6 enzymes Found in the liver and central nervous system, specifically in Substantia nigra, is responsible for the metabolism of foreign biological substances Xenobiotics in the body[18.19] as these enzymes are considered a mediator in the process of metabolizing codeine into morphine, which causes increased morphine leakage into the dorsal raphe nucleus in rats, the amount of codeine that is metabolized into morphine does not depend on the amount of codeine ingested but on the ability to convert it by action. CYP_2D_6 enzymes, which are present in large quantities in people with a high metabolism and a smaller proportion in people with low metabolism. It reflects the possibility of some resistance to resisting the sedative effect of opioids more than others, and the higher the concentration of morphine, the greater the ability to bind to mu-opioid receptors, and thus the possibility of producing mu-opioid receptors. Active secondary metabolites have the potential to increase the efficacy of the production of high concentrations of hormones and neurotransmitters from pre-synaptic cells and their accumulation in the synaptic cleft such as serotonin.[20,21]

Histopathological Results and Disscation

1. *Control Group:* The liver appeared in the control group. Contain the liver lobular and each lobule contains a large



Histogram Showing the Effect of Tramadol, Pseudoephedrine, and Codeine Phosphate on Serotonin Concentrations.

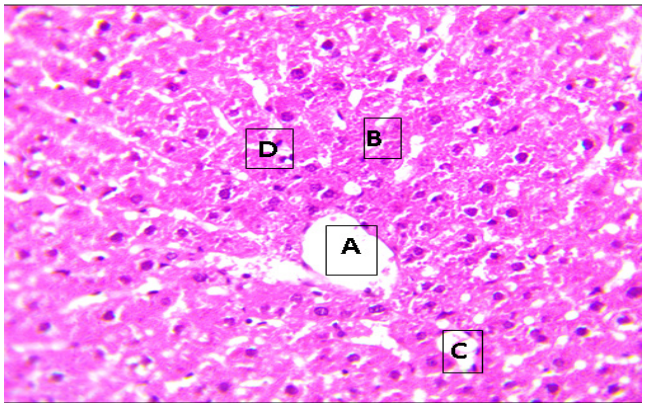


Image 1: Hepatic lobule in the control group: Central vein (A), rows of hepatocytes (B), hematopoietic (C), coffer cells (D), examined with X40 magnification force, colored with H&E

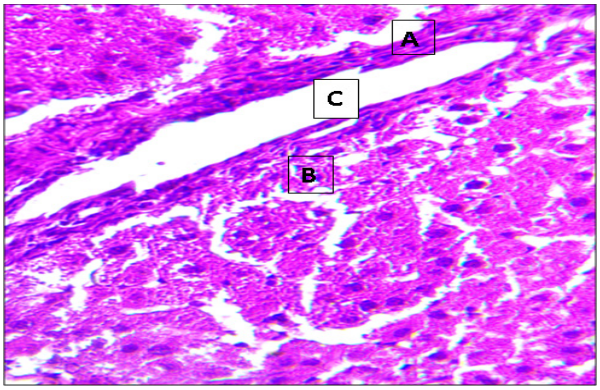


Image 2: Liver parenchyma in the group treated with tramadol: (A) enlarged liver cells, (B) hepatocyte degeneration, (C),central vein examined with X40 magnification, colored with H&E.

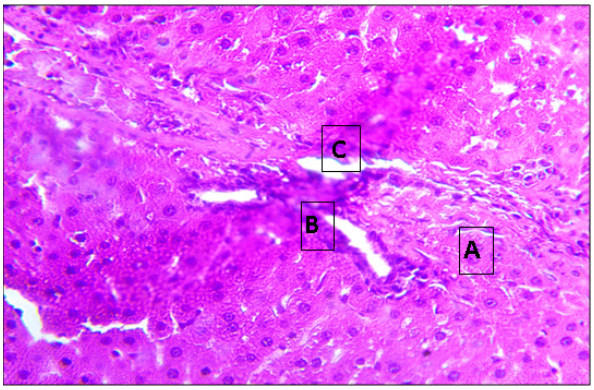


Image 3: Liver parenchyma in the group treated with pseudoephedrine: hepatocyte enlargement (A), lymphocyte infiltration in the portal area (B), bile duct (C), examined with X40 magnification, colored with H&E.

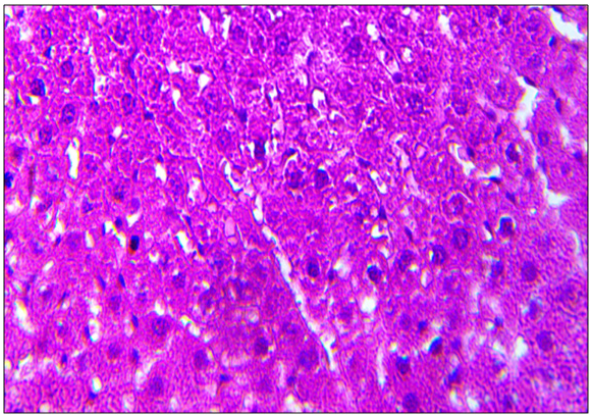


Image 4: The liver parenchyma in the group treated with the drug codeine phosphate: shows hepatocyte enlargement and thickening of the nuclei, examined with X40 magnification, colored with H&E.

number of liver cells. Each cell appeared polygonal and large, with a nucleus or two dark-colored nuclei surrounded by the acid-pigment cytoplasm. Towards the center of the lobule, in which the central vein was found, the sinusoid blood vessels that extend between the bundles and rows of hepatocytes and Kuepfer cells appeared inside the hepatic sinuses

2. *Tramadol Group:*.The liver parenchyma appeared to contain enlarged liver cells in some areas and degenerative cells that lost their nuclei in other areas, as shown in Image 2.
3. *Pseudoephedrine Group:* The liver parenchyma appeared contained excessively enlarged liver cells, as shown in Image 3.
4. *Codeine phosphate*: The liver parenchyma with enlarged cells and enlarged nuclei as shown in Image 4.

The use of opioids was and still is widespread, which often has significant effects, especially in the long term. The group treated with the drug tramadol showed the occurrence of enlargement of some hepatocytes and degeneration of other cells that lost their nuclei in several areas of liver tissue, which may return To increase the cellular activity of the liver tissue as an attempt to combat the toxicity caused by the drug tramadol. Thus, the results of this study are in agreement with a study.[22] which showed that treatment with tramadol increases the activity of hepatocytes and causes toxicity and damage to cells. Hepatic tissue and an increased incidence of fibrosis in liver tissue and the bile ducts within the liver. The liver in the group treated with the drug pseudoephedrine showed significant tissue damage that was characterized by the leaching of white blood cells, especially the lymphocytes, which had accumulated significantly in the

portal region around the portal vein, hepatic artery, and the bile duct. It is very similar to adrenaline in its composition and pharmacological effects. Thus, pseudoephedrine is a catalyst for the production of TNF-a and increasing the likelihood of developing autoimmune diseases. Thus, the results of this study agree with the study[23] which showed that the drug pseudoephedrine can contribute. In translating cytokines from their coding genes, which in turn produce necrosis factors such as tumor necrosis factor. The liver in the group treated with the drug codeine phosphate showed tissue damage characterized by the enlargement of some hepatocytes in some areas of the tissue, as well as the thickening of some nuclei, that the liver tissue represents the tissue most affected by the drugs used due to the attempt of the hepatocytes to maintain the internal balance. In line with the external influences represented by drugs and the internal changes occurring to them, and the cells' attempt to adapt to these changes, especially if the changes exceed the normal limit, as the cells may make adjustments in their structural or functional structure, such as an increase in the size of the cell, hypertrophy, or a change in the size of the nuclei and their congestion.[24]

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