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A Histopathological Study of the Therapeutic Role of Kisspeptin-10 Against Cadmium Chloride Toxicity in Rats

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Abstract

Kisspeptin is originally a metastasis suppressor. Currently, post preliminary discovery, the crucial physiology of kisspeptin appeared among several biological function in the living body such as supporting the reproductive system, regulation the metabolism, improvement the cardiac muscle action and smooth muscle of blood vessels. Moreover, Kisspeptin play an important role as a neurotransmitter through the Kisspeptin receptor. This study is designed to examine the anti-toxic role of Kisspeptin in some vital organs including the liver, spleen, and kidney. Kisspeptin is demonstrated as a detoxification agent via the elimination of toxicity of cadmium chloride to some organs of living rats such as the liver, spleen, and kidney. Direct negative effects of Kisspeptin on these organs have only been recognized. This study attempts to explain this role during the examination of histopathological changes in the case of cadmium chloride toxicity and the effect of Kisspeptin in reducing or elevating the toxicity after its administration in both 20 and 40 nanomolar / animal doses. Arguments and recent boundaries in the field, as well as areas of coming research related to kisspeptin's varied function array, should underline.

Keywords: *Kisspeptin-10, Histopathology, Cadmium Chloride toxicity*

1. Introduction

Kisspeptins encoded by the gene of *KISS1* gene, have been classified as neuropeptides that are first recognized as metastasis suppressors, and play significant regulatory roles for reproduction (Pinilla *et al*., 2012). In the hypothalamus, double main neuron populations have been distinguished to produce kisspeptin: the rostral periventricular area 3rd ventricle (RP3V) and arcuate nucleus (ARC). These populations are programmed and activated neurons of gonadotropin-releasing hormone (GnRH), leading to the release and production of GnRH. Gonadal sex hormones catalyze the RP3V Kisspeptin neurons whereas inhibit the activity of ARC Kisspeptin neurons. This is considered a fundamental

pathway for positive and negative feedback regulation; and recently, it has been accepted to prove that GnRH secretion is activated by the ARC Kisspeptin neurons (Harter *et al*., 2018; Huda *et al*., 2022). Reproduction has been regulated via a complex interplay between neural and hormonal indicating that assembles on hypothalamic neurons that realize the pulsatile secretion of GnRH (Marques *et al*., 2022; Walaa *et al*., 2022).

Cadmium (Cd), heavy metal of high toxicity, has damaging effects on organs in the living body, and is extensively disseminated in humans due to exposure to main sources of contamination that come from smokes of cigarettes, contaminated food and beverages, and welding. The toxicity of Cd has been detailed and appeared proportional, and explained to be absorbed more efficiently by the lungs than the gastrointestinal tract (Nordberg *et al*., 1985; Robin, 2013). This metal can be transported in the blood, circulated extensively in the body, and accumulated mainly in the liver and kidney (Goyer, 1991). The burden of this metal is inclined to increase gradually with age (ATSDR, 1989).

2. Materials and Methods

Experimental Animals

Forty male rats will be divided into two groups the first group ten adult male rats were IP injected with distal water once /week for two weeks to serve as a control group. While the second group included thirty male rats have been induced testicular degeneration (TDS) by intraperitoneal injection (IP) of cadmium chloride 1mg/kg B.W. once /week for two weeks according to a Pilot study to induce testicular degeneration syndrome (Al-Sharafi and Alobaidy, 2022). At the end of the experiment period, 5 male rats from each group will be sacrificed for the histopathological study of liver, kidney, and spleen. The remainder animals from the above period (5 rats will be kept as the control group and 25 rats from the testicular degeneration group) will be divided into four as follows first group control group five adult male rats were S/C injected with sterile distal water solution twice/week every 72 hours, the second group Cadmium Chloride group five male rats will be selected randomly and untreated from testicular degeneration were S/C injected with sterile distal water solution twice / week every 72 hours, third group ten rats from testicular degeneration will be treated with 20 nanomolar / animal of Kisspeptin 10 by s/c every 72 hours, while the forth ten rats from testicular degeneration will be treated with 40 nanomolar / animal of Kisspeptin 10 by s/c every 72 hours the experiment extend for 30 days after that the animals would be sacrificed for the histopathological study of liver, kidney, and spleen.

Organ Collection and Histopathological Examination

Three organs were collected from sacrificed animals, liver, kidney and spleen. After cutting into small pieces, a $5mm^3$ from each organ was washed with PBS and fixed with 10% formalin and kept in clean cups. After 24 hrs, the 10% formalin was then changed to a fresh one to ensure that concentration is preserved at 10%. Subsequently, the fixed tissues were dehydrated throughout the passing theme in different ethanol concentrations of 75%, 85%, 95%, 100%, and 100% for one hour to each respectively. Thereafter, the tissues have been immersed in xylene three different times for one hour each. Lastly, the tissues were fixed in liquid paraffin at 60°C. Previously, the samples of tissues were embedded in tissue cassettes with liquid paraffin. Finally, the blocks have been cutting into 5-micron slices using a microtome and fixed on glass slides.

For staining, hematoxylin and eosin staining protocol was followed as serial steps, deparaffinization at 65°C for 30 min.; and then, tissues were immersed in xylene for 10 minutes two times. Subsequently, rehydration processes were applied to the tissue by immerse of sections in 100% ethanol for 5 minutes, and followed by immersion in 100%, 95%, 85%, and 75% of ethanol for 5 min., respectively. Thereafter, the sections have been rinsing in distilled water for 5 min., dried at room temperature for 1-2 min., and staining theme with hematoxylin for 5 min., following washing with distilled water for 5 min., and staining the sections with eosin for 3 min.

The dehydration of sections was followed by immersing the tissues in 75%, 85%, 95%, and 100% for 5 min. to each respectively. Then, the sections were immersed in xylene twice for 5 min. each and clear theme and mount coverslips with neutral mounting media such as DPX.

3. Results and Discussion:

Histopathological Lesions

The histopathological changes in organs were examined using a light microscope. The liver, kidney and spleen showed different lesions in their texture. The organs in the control negative group showed normal texture without any significant occupied lesions (SOL) (Figures 1-4). In the cadmium chloride group (positive control group), the spleen showed clear hyperplastic changes and blood vessel congestion (Figures 5 and 6). In addition, severe to highly severe amyloidosis has been shown in the red pulp of the spleen due to cadmium chloride toxicity as shown in Figure 7.

The renal tissue explained clear renal vein congestion and moderate glomerular tuft atrophy and increasing glomerular space. The renal proximal tubules showed severe epithelial cell hypertrophy with narrowing of the tubular lumen with mild fiber network formation in the renal parenchyma. Some areas of renal texture showed moderate glomerular tuft atrophy and increasing glomerular space (Figures 8-10). Moreover, severe and highly severe renal damage show amyloid degenerative changes in the renal tubules and clear damage in the renal vein wall with narrowing in the ureter. As highly severe damage in the renal tissue, the fibrous network has been seen in the renal parenchyma causing clear damage in the proximal renal tubules (Figures 11-13).

The histopathological changes in the liver in rats treated with cadmium chloride showed hepatic vein congestion with hepatocellular cloudy swelling (parenchymatous degenerative changes). Furthermore, the hepatic section shows severe changes via deposition of a structureless, homogenous and pinkish proteinous material (amyloidosis) (Figure 14). Additionally, the hepatic tissue section showed clear thrombus formation in the hepatic vein and perivascular cuffs of leucocytes that appear as severe damage in the hepatic parenchyma (Figure 15). The hepatic section showed a deposit of a network of fibrin surrounding the hepatic blood vessels (vein and artery), and the hepatic section showed clear sinusoidal space dilation and severe aggregation of mononuclear inflammatory cells (Neutrophils), (Figure 16). In addition, the hepatic tissue explained highly severe fatty degenerative lesions due to cadmium chloride toxicity (Figure 17).

Subsequently, Kisspeptin-10 was administrated after 14 days of toxicity induction by cadmium chloride. Two groups of experimental animals have been subcutaneously injected with Kisspeptein -10, the first one was injected with 20 nano molar/animal and the second group was injected with 40 nanomolar / animal respectively every 72 hours, throughout 30 days of the experimental period. The splenic tissue showed a clear reduction in the size of the lymphocytes aggregation area (White pulp) for both doses of Kisspeptin-10 (20 and 40 nano molar/animal) (Figures 18-21). Similarly, for the liver and kidney, the tissue textures showed clear regenerative changes in the hepatocytes and nephrons (Glomerulus and renal tubules) after treatment with Kisspeptin-10 for both doses (20 and 40 nanomolar/animal). The sinusoidal hepatic space and hepatocytes enhanced to back to normal texture during the period of treatment. The hepatic tissue demonstrated no significant occupied lesion (SOL), (Figures 22, 23). In the same manner, Kisspeptine-10 enhanced the renal tissue repair and elimination of the toxic effect of CDCL2 on renal tissue (Figures 24-26).

Tissue Damage Scoring

To evaluate the degree of tissue damage, the scoring protocol has been followed (Zingarelli *et al*., 1998; Gibson-Corley *et al*., 2013). Ten rats from each group have been involved and three tissue sections (spleen, liver and kidney) from each rat were scored to evaluate the degree of damage (Figure 27, Tables 1-3). The results of scoring showed that cadmium chloride induced severe and highly severe lesions in the vital organs compared to the control, while the treated animals with Kisspeptin-10 in both 20 and 40 nanomolar explained regenerative changes in these organs and retiring to the normal state after treatment comparing to the cadmium chloride animal group. The tissues were back from severe and highly severe status due to cadmium toxicity to mild and healthy condition, which showed no significant occupied lesions (No SOL). These outcomes explain a significantly decreasing in the level of tissue damage after treatment with Kisspeptin-10 in both doses 20 and 40 nanomolar (Figure 27).

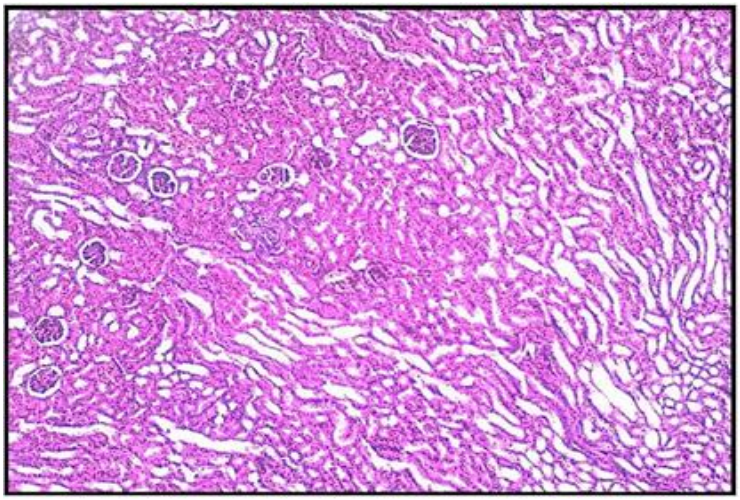

Figure 1. Histopathological section in the kidney in control group. The section shows normal histological texture in the renal tissue (renal glomeruli and tubules) without any significant occupied lesion (SOL). H&E stain, 4X. Source: Authors.

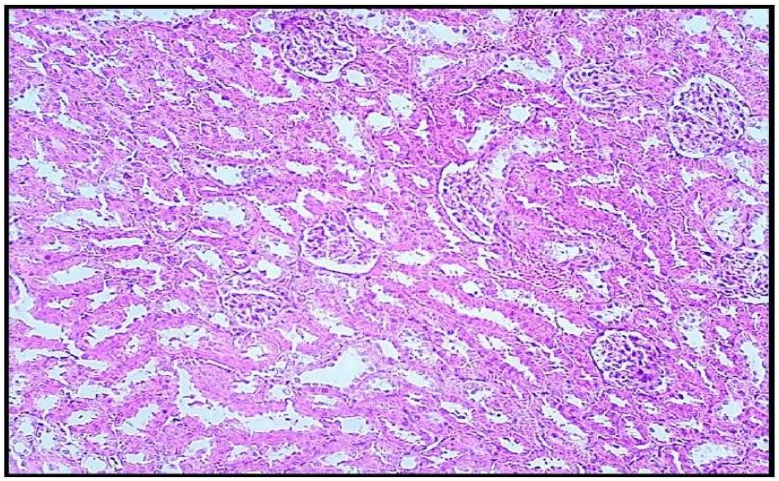

Figure 2. Histopathological section in the kidney in control group. The section shows normal histological texture in the renal tissue (renal glomeruli and tubules) without any significant occupied lesion (SOL). H&E stain, 10X. Source: Authors.

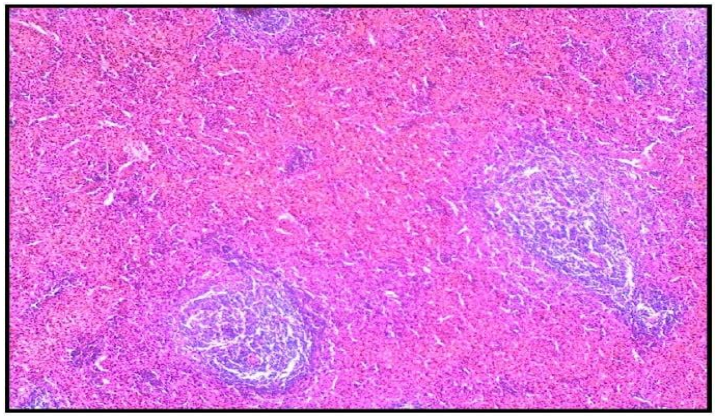

Figure 3. Histopathological section in the spleen in control group. The section shows normal histological texture in the spleen tissue (White and Red pulp) without any significant occupied lesion (SOL). H&E stain, 10X. Source: Authors.

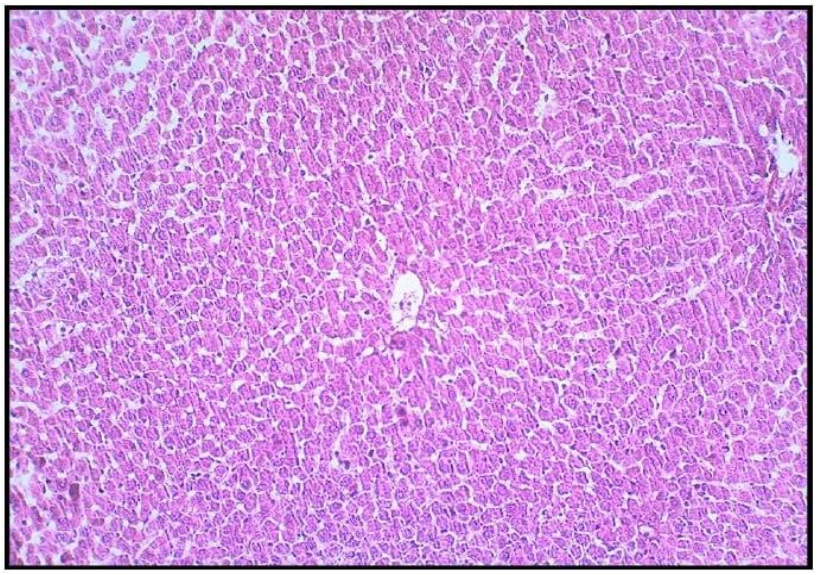

Figure 4. Histopathological section in the liver in control group. The section shows normal histological texture in the hepatic tissue (hepatocytes and sinusoidal section) without any significant occupied lesion (SOL). H&E stain, 10X. Source: Authors.

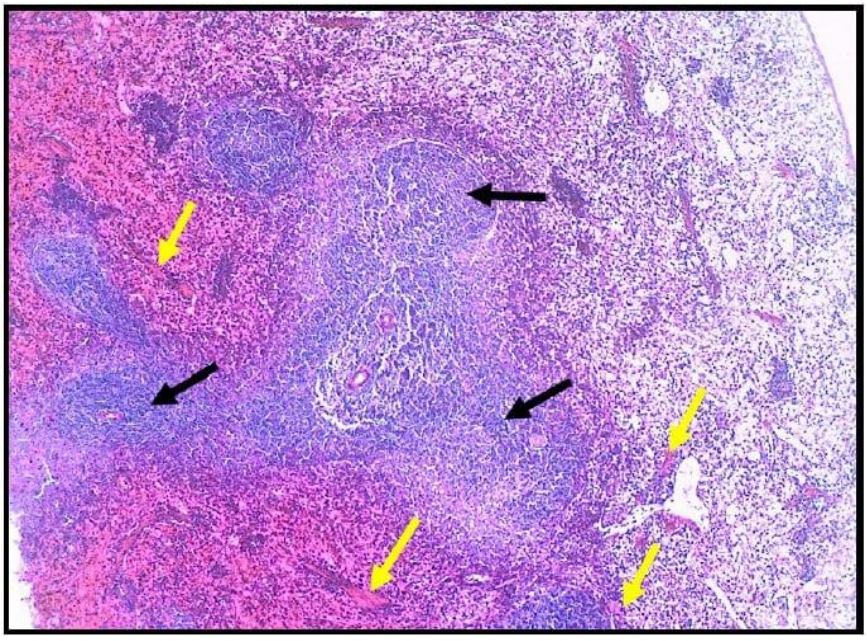

Figure 5. Histopathological section in the spleen of rats that treated with CDCL2 (1 mg / kg B.W.) in the induction group. The section shows sever reactive hyperplasia in lymphoid nodule (white pulp, Black arrows) with congestion in pulp arteries can be seen in different area of splenic section (Yellow arrows). H&E stain, 10X. Source: Authors.

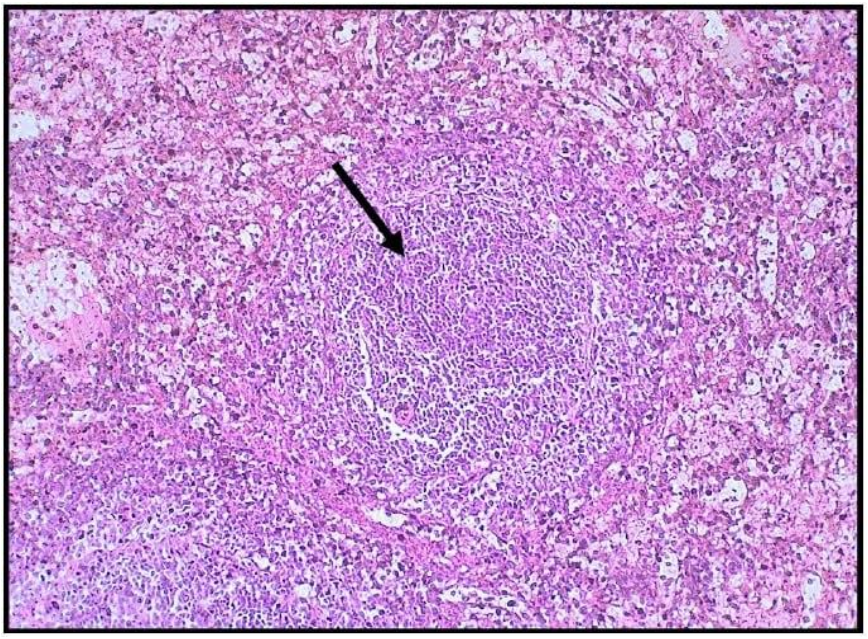

Figure 6. Histopathological section in the spleen of rats that treated with CDCL2 (1 mg / kg B.W.) in the induction group. The section shows sever reactive hyperplasia in lymphoid nodule (white pulp, Black arrow). H&E stain, 20X. Source: Authors.

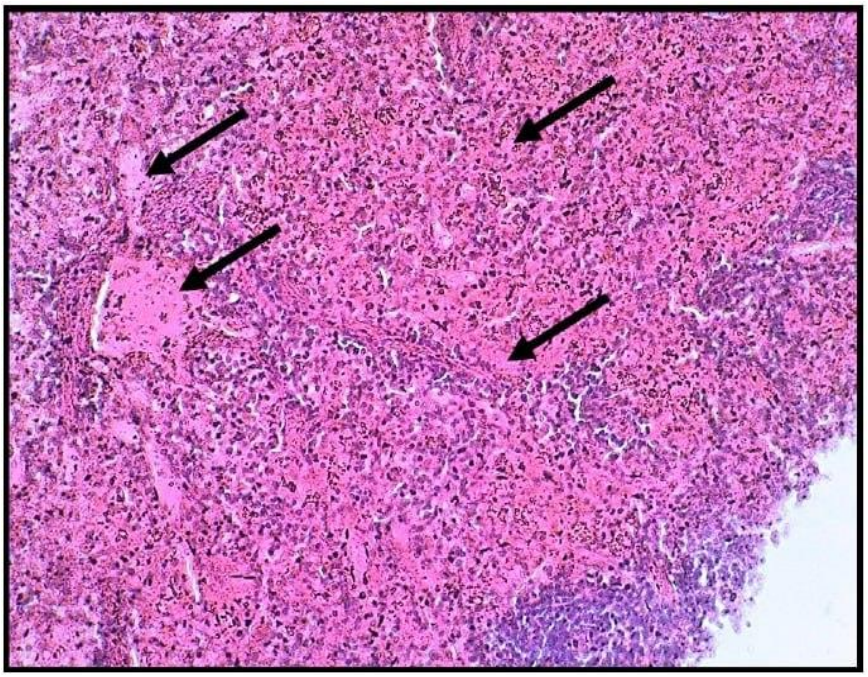

Figure 7. Histopathological section in spleen of rats that treated with CDCL2 (1 mg / kg BW) in the induction group. The section shows sever – highly sever amyloid protein infiltration (amyloidosis, amyloid degeneration, Black arrows) in the red pulp and blood vessels. H&E stain, 10X. Source: Authors.

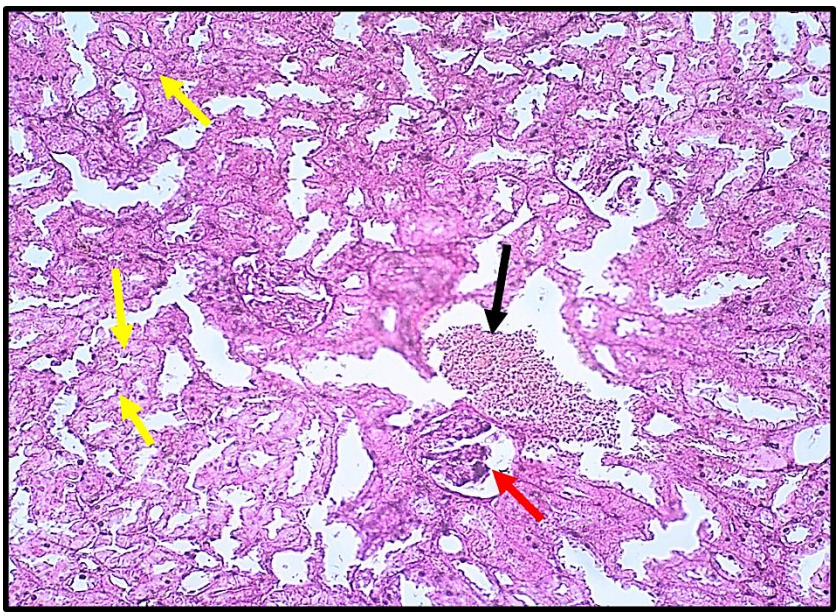

Figure 8. A histopathological section in the kidney of a rat treated with CDCL2 (1mg/kg B.W.). The section shows clear renal vein congestion (Black arrow) and moderate glomerular tuft atrophy and increasing glomerular space (Red arrow). The renal proximal tubules show severe epithelial cell hypertrophy with narrowing of the tubular lumen (Yellow arrows). H&E stain, 10X. Source: Authors.

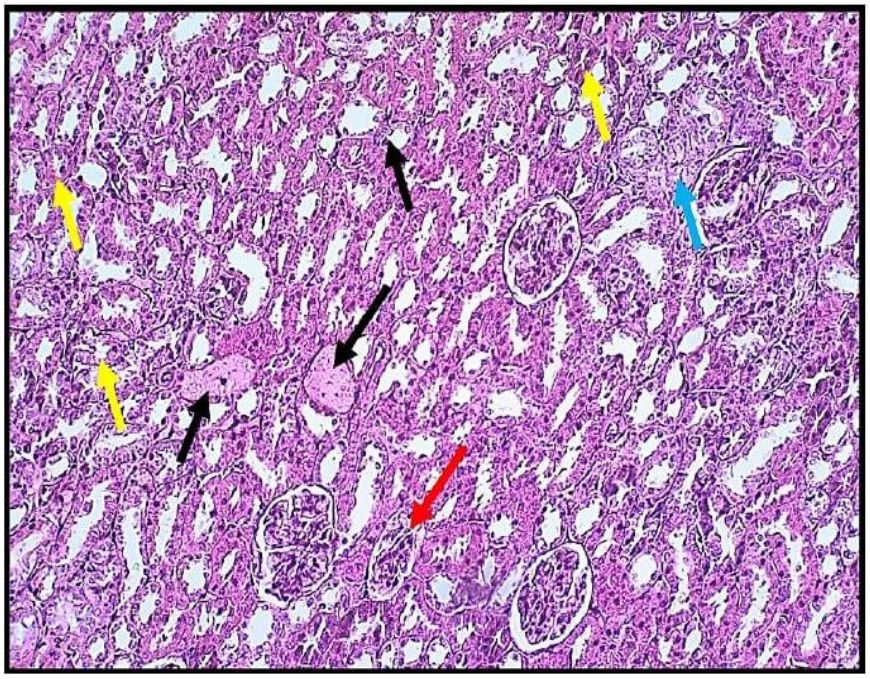

Figure 9. A histopathological section in the kidney of a rat treated with CDCL2 (1mg/kg B.W.). The section shows clear renal vein congestion (Black arrows) and moderate glomerular tuft atrophy (Red arrow). The renal proximal tubules show mild epithelial cell hypertrophy with narrowing of the tubular lumen (Yellow arrows) with mild fiber network formation in the renal parenchyma (blue arrow). H&E stain, 10X. Source: Authors.

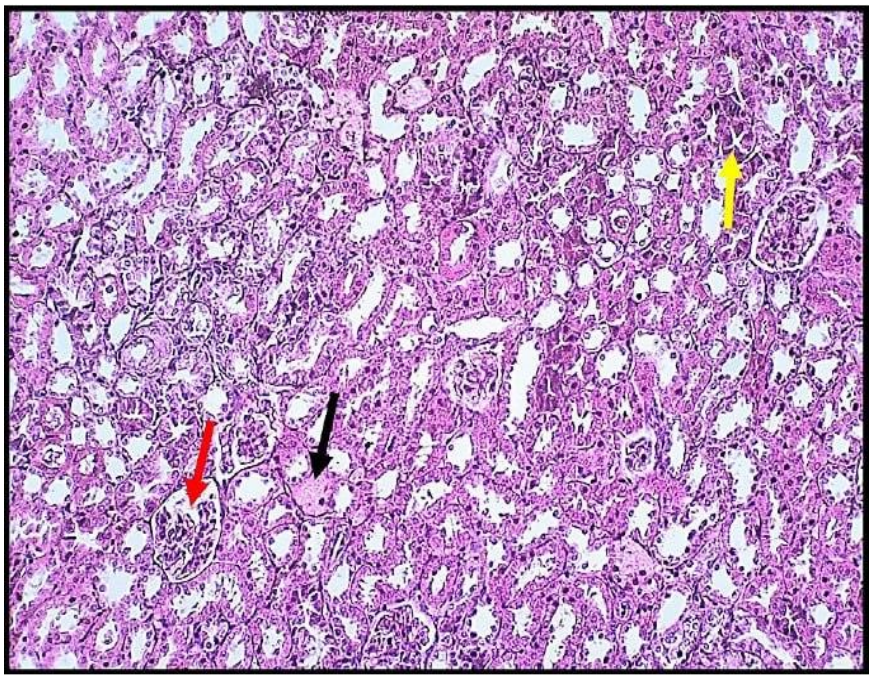

Figure 10. A histopathological section in the kidney of a rat treated with CDCL2 (1mg/kg B.W.). The section shows clear renal vein congestion (Black arrow) and moderate glomerular tuft atrophy and increasing glomerular space (Red arrow). The renal proximal tubules show mild epithelial cell hypertrophy with narrowing of the tubular lumen (Yellow arrows). H&E stain, 10X. Source: Authors.

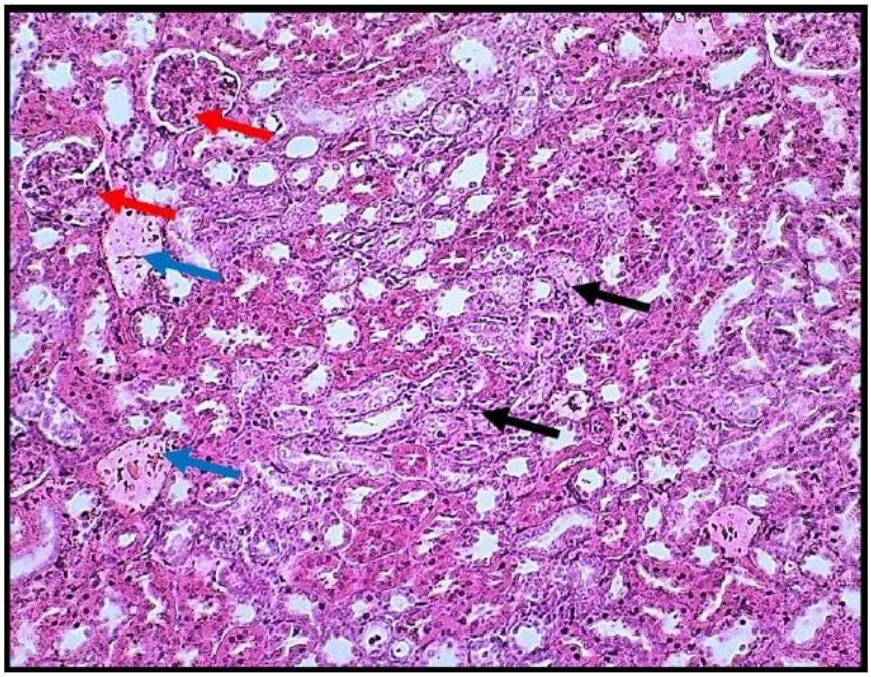

Figure 11. A histopathological section in the kidney of a rat treated with CDCL2 (1mg/kg BW). The section shows severe infiltration of amyloid protein in the renal tubules (amyloid degeneration, amyloidosis Black arrows) and renal proximal tubules (Red arrows) with the renal vein (Blue arrows). H&E stain, 10X. Source: Authors.

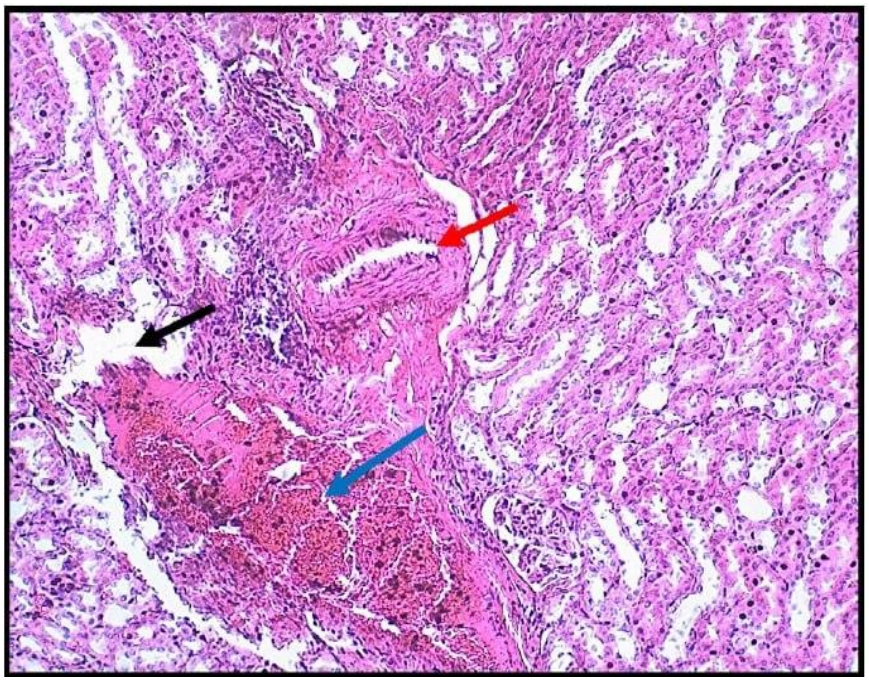

Figure 12. A histopathological section in the kidney of a rat treated with CDCL2 (1mg/kg BW). The section shows highly severe damage in the renal vein wall (Black arrow) with congestion of the renal vein (Blue arrow). The renal ureter shows clear narrowing in the lumen due to reactive hyperplastic changes in the epithelial cell of the ureter (Red arrow). H&E stain, 10X. Source: Authors.

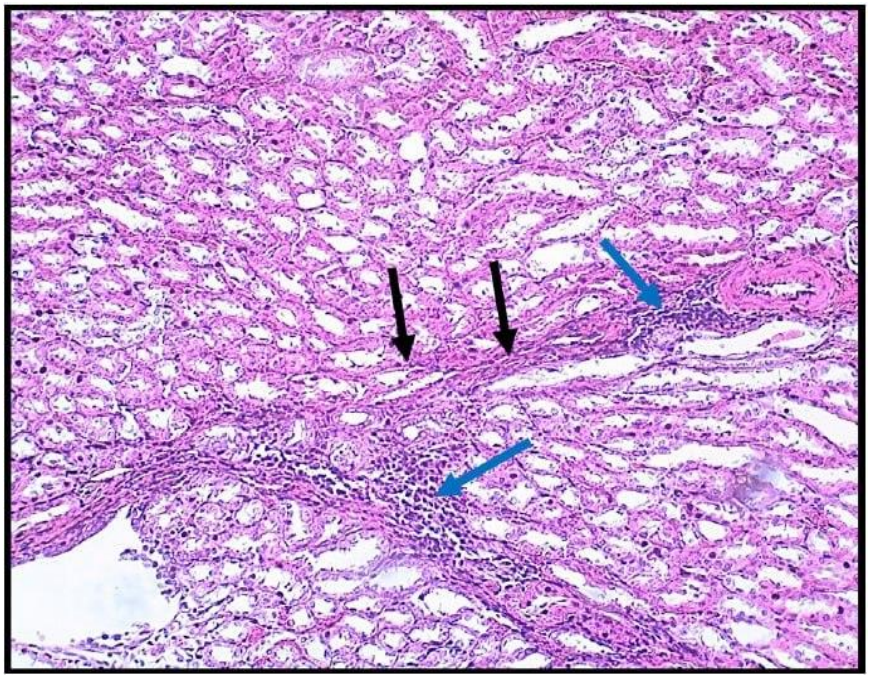

Figure 13. A histopathological section in the kidney of a rat treated with CDCL2 (1mg/kg BW). The section shows highly severe damage in the proximal renal tubules (Black arrows) due to the formation of a network of fibrous connective tissue with aggregation of inflammatory cells (Mainly neutrophils and macrophages, blue arrows). H&E stain, 10X. Source: Authors.

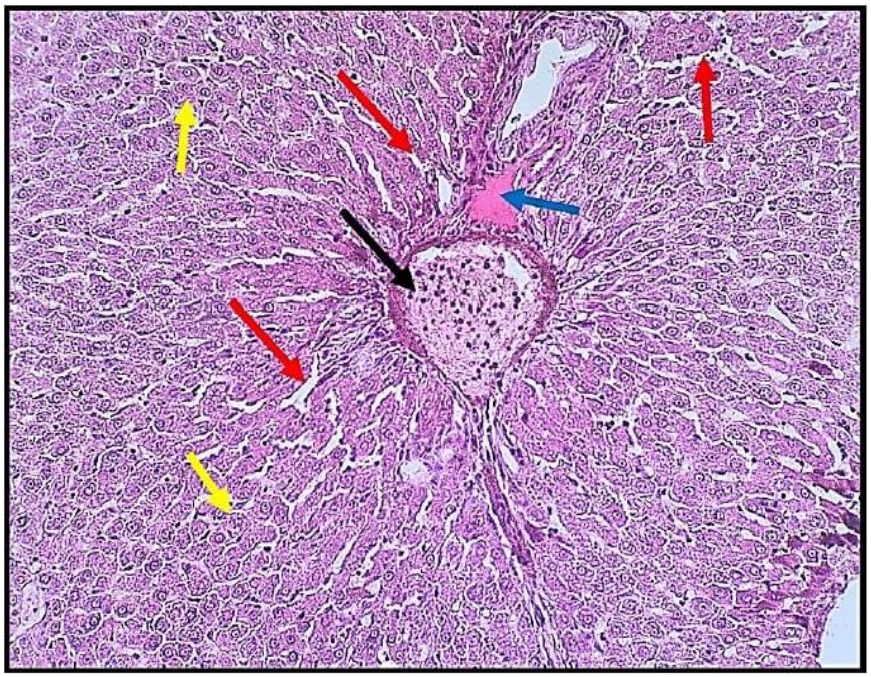

Figure 14. A histopathological section in the liver of a rat treated with CDCL2 (1mg/kg B.W.). The section shows hepatic vein congestion (Black arrow) and mild sinusoidal space increasing (Red arrows) with hepatocellular cloudy swelling (parenchymatous degenerative changes, yellow arrows). The section shows the deposit of a structureless, homogenous and pinkish material (amyloidosis, blue arrow). H&E stain, 10X. Source: Authors.

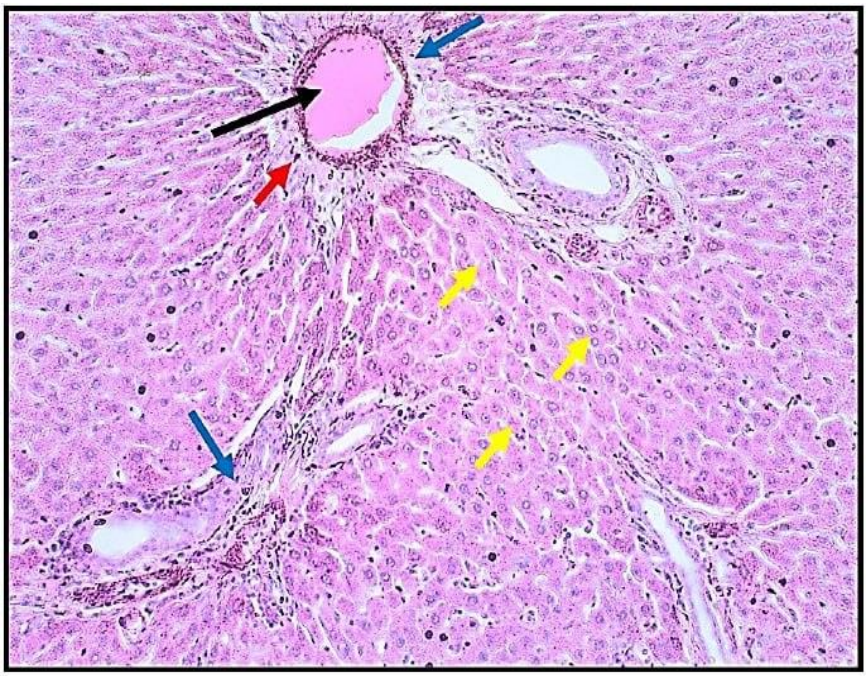

Figure15. A histopathological section in the liver of a rat treated with CDCL2 (1mg/kg B.W.). The section shows clear thrombus formation in the hepatic vein (Black arrow) and perivascular cuffs of leucocytes (Red arrow) with hepatocellular cloudy swelling (parenchymatous degenerative changes, yellow arrows). The section shows the deposit of a network of fibrin surrounding the hepatic blood vessels (vein and artery, blue arrows). H&E stain, 10X. Source: Authors.

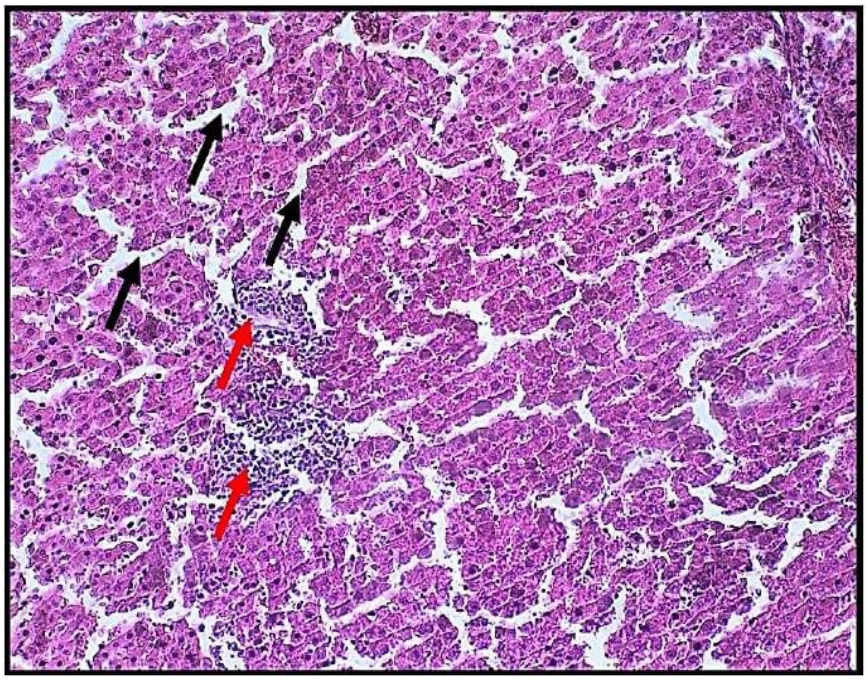

Figure 16. A histopathological section in the liver of a rat treated with CDCL2 (1mg/kg B.W.). The section shows clear sinusoidal space dilation (Black arrows) and aggregation of mononuclear inflammatory cells (Neutrophils, Red arrow). H&E stain, 10X. Source: Authors.

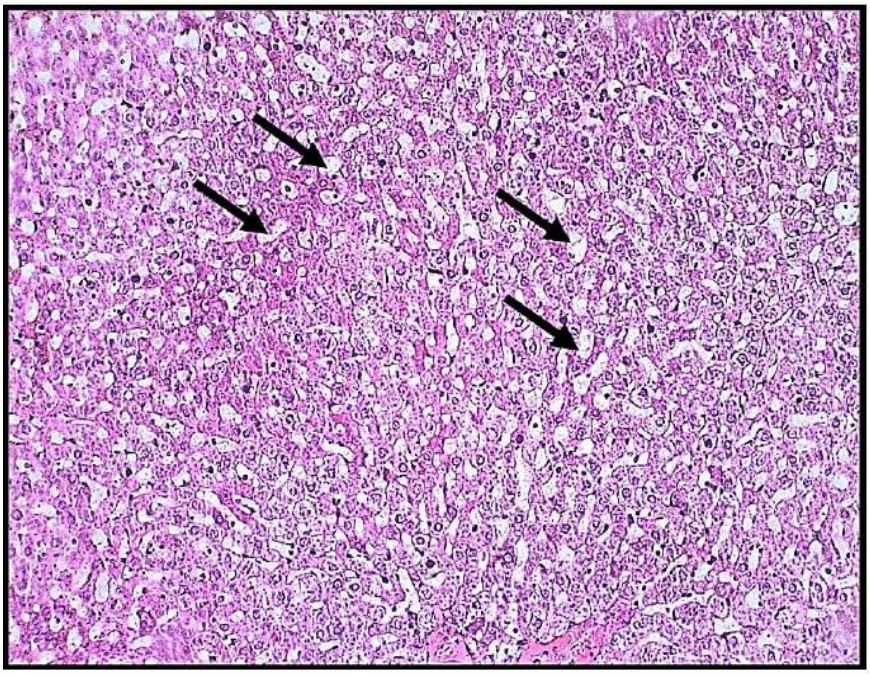

Figure17. A histopathological section in the liver of a rat treated with CDCL2 (1mg/kg B.W.). The section shows clear fat droplets infiltration in the cytoplasm of hepatic cells (Black arrows). H&E stain, 20X. Source: Authors.

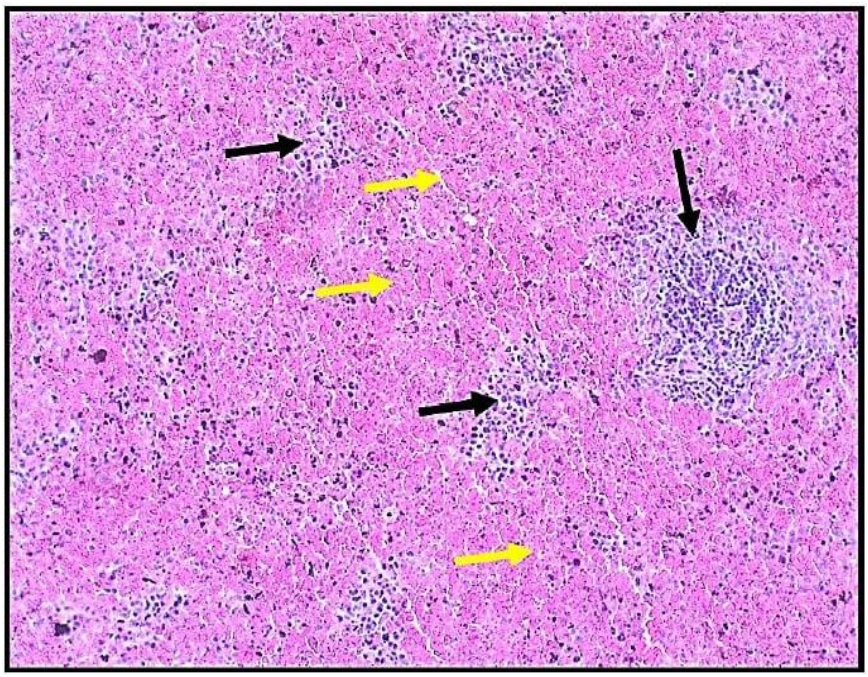

Figure 18. A Histopathological section of spleen in a rat treated with 20 nM of Kisspeptin after CDCL2 intraperitoneal injection (1mg/kg BW). The section shows normal lymphocyte aggregation area (White pulp, Black arrows) and red pulp shows normal splenic (Blood) sinusoidal area (Yellow arrows). H&E stain, 10X. Source: Authors.

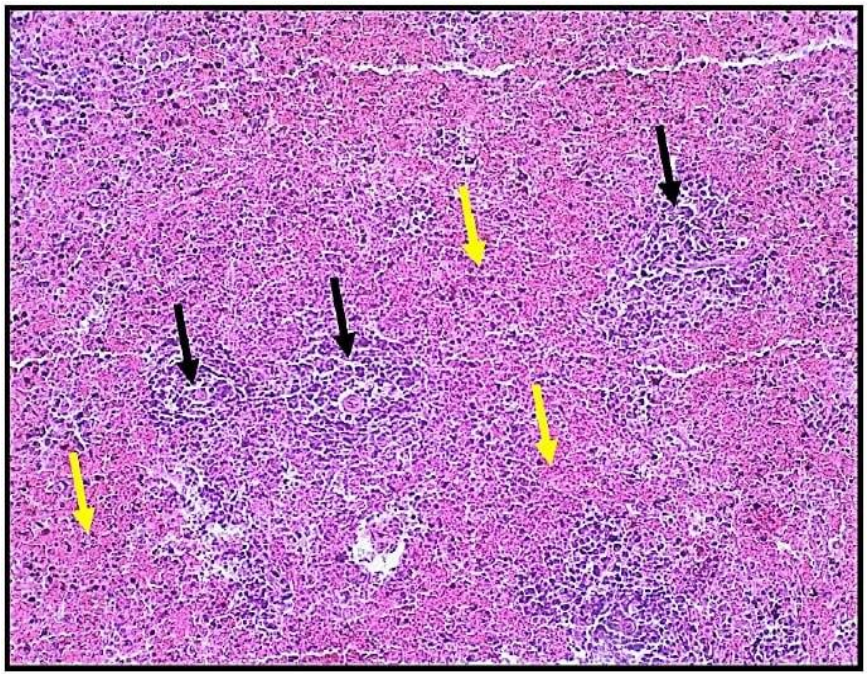

Figure 19. A Histopathological section of the spleen in a rat treated with 40 nM of Kisspeptin after CDCL2 intraperitoneal injection (1mg/kg BW). The section shows normal lymphocytes aggregation area (White pulp, Black arrows) and red pulp shows normal splenic (Blood) sinusoidal area (Yellow arrows). H&E stain, 10X. Source: Authors.

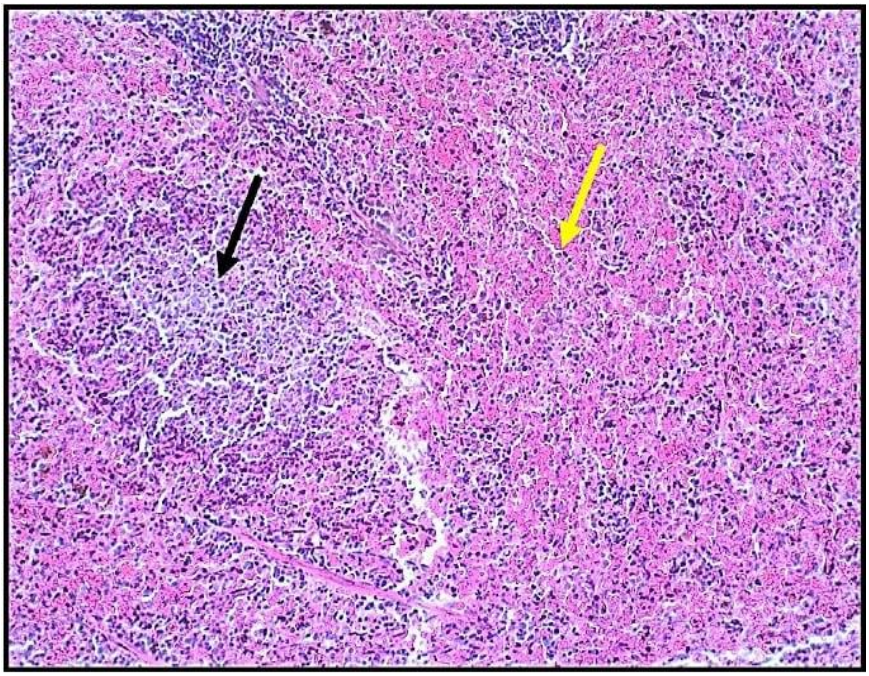

Figure 20. A Histopathological section of spleen in rat that treated with 20 nM of Kisspeptin after CDCL2 intraperitoneal injection (1mg/kg B.W.). The section shows normal lymphocytes aggregation area (White pulp, Black arrow) and red pulp shows normal splenic (Blood) sinusoidal area (Yellow arrow). H&E stain, 20X. Source: Authors.

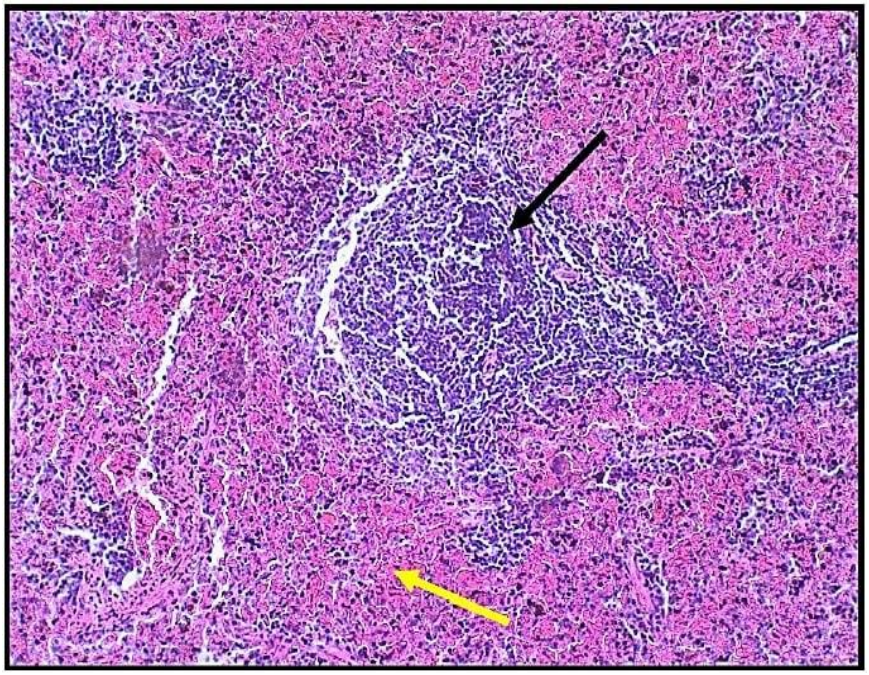

Figure 21. Histopathological section of spleen in rat that treated with 20 nM of Kisspeptin after CDCL2 intraperitoneal injection (1mg/kg BW). The section shows normal lymphocytes aggregation area (White pulp, Black arrow) and red pulp shows normal splenic (Blood) sinusoidal area (Yellow arrow). H&E stain, 20X. Source: Authors.

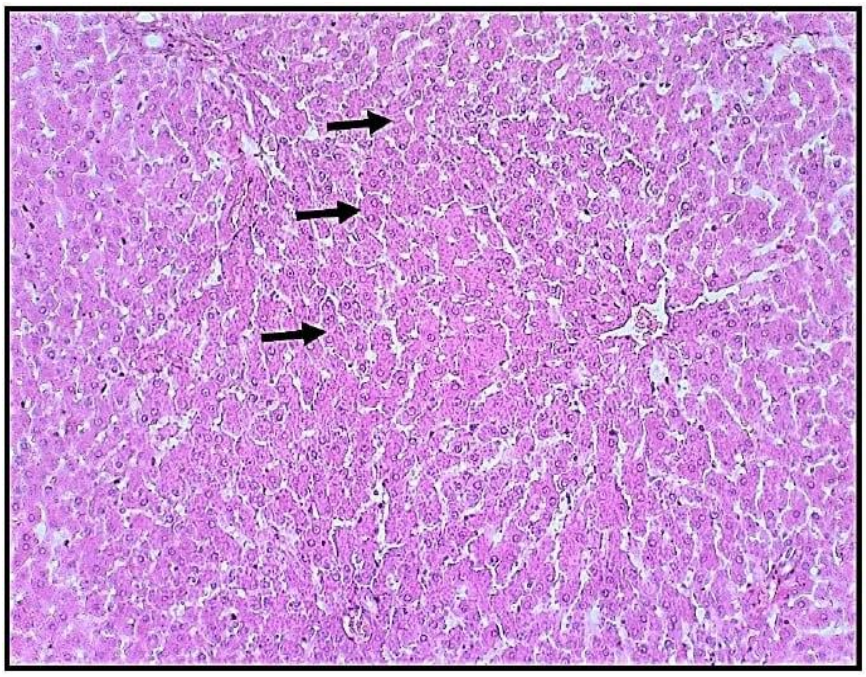

Figure 22. Histopathological section of liver in rat that treated with 20 nM of Kisspeptin after CDCL2 intraperitoneal injection (1mg/kg BW). The section shows normal hepatic tissue texture and normal hepatocytes without any significant occupied lesion (SOL) (Black arrows). H&E stain, 10X. Source: Authors.

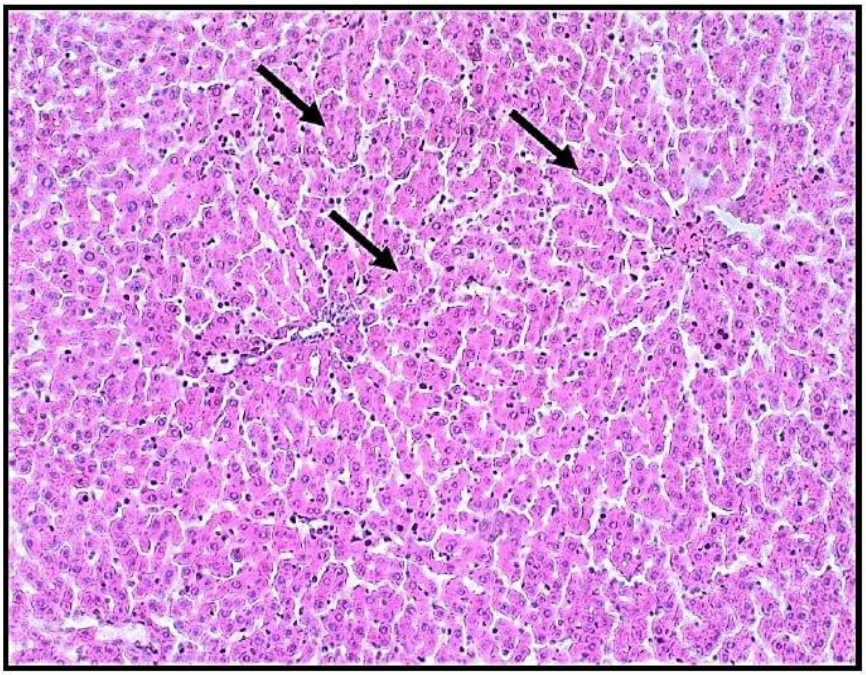

Figure 23. Histopathological section of liver in rat that treated with 40 nM of Kisspeptin after CDCL2 intraperitoneal injection (1mg/kg B.W.). The section shows normal hepatic tissue texture and normal hepatocytes without any significant occupied lesion (SOL) (Black arrows). H&E stain, 10X. Source: Authors.

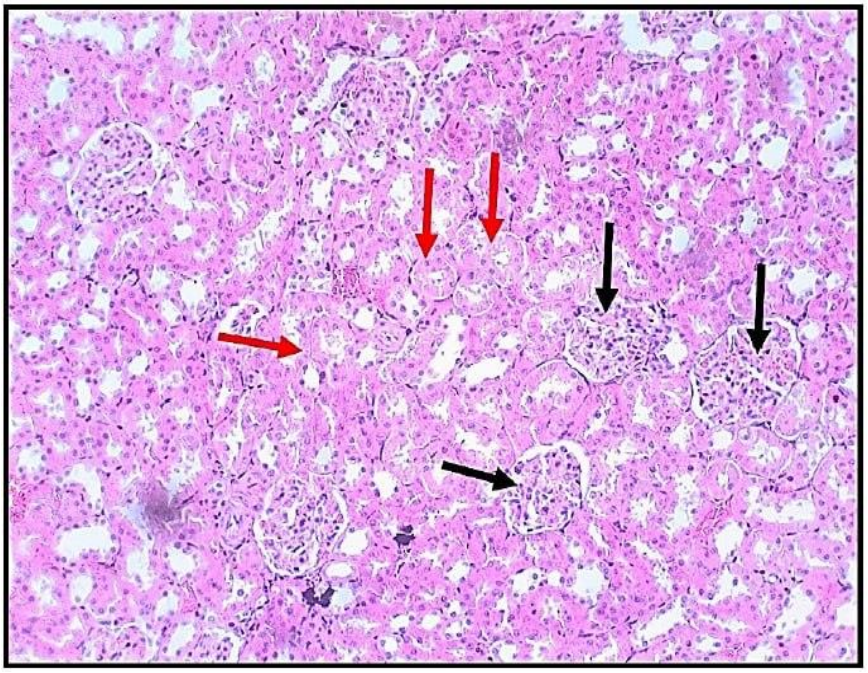

Figure 24. Histopathological section of kidney in rat that treated with 20 nM of Kisspeptin after CDCL2 intraperitoneal injection (1mg/kg B.W.). The section shows normal renal tissue texture (Renal glomeruli, Black arrows and renal proximal tubules, Red arrows). H&E stain, 10X. Source: Authors.

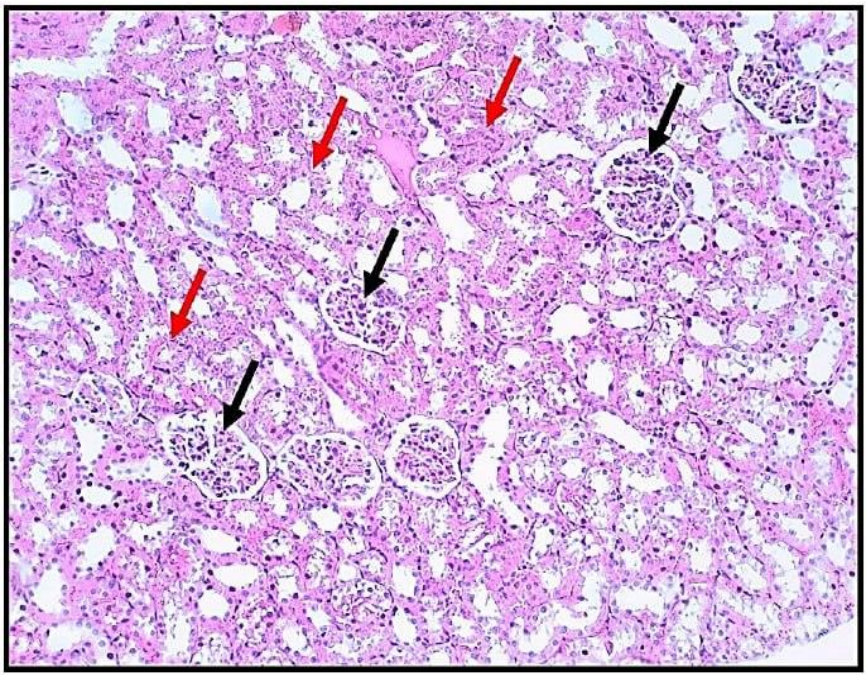

Figure 25. Histopathological section of kidney in rat that treated with 20 nM of Kisspeptin after CDCL2 intraperitoneal injection (1mg/kg B.W.). The section shows normal renal tissue texture (Renal glomeruli, Black arrows and renal proximal tubules, Red arrows). H&E stain, 10X. Source: Authors.

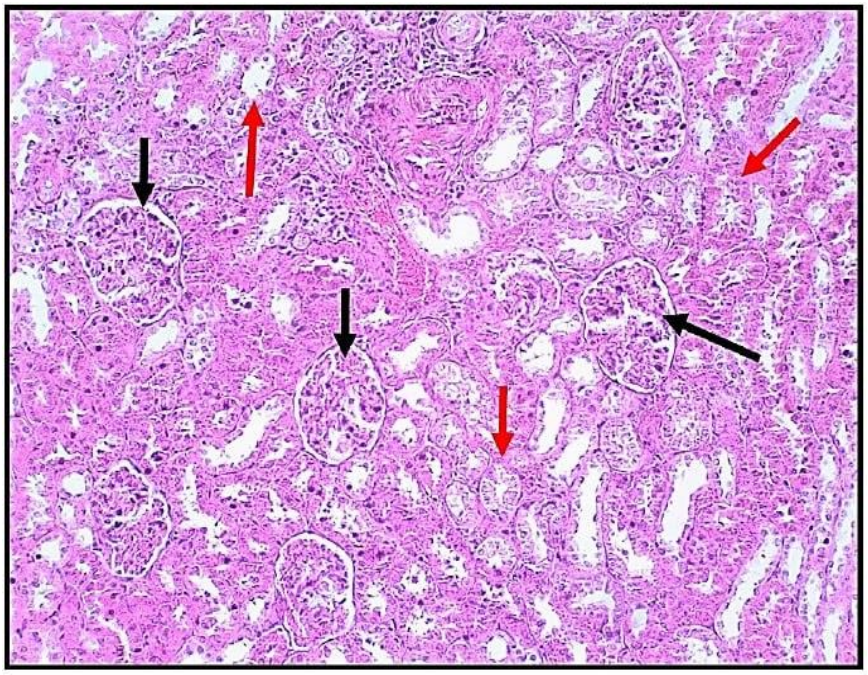

Figure 26. Histopathological section of kidney in rat that treated with 40 nM of Kisspeptin after CDCL2 intraperitoneal injection (1mg/kg BW). The section shows normal renal tissue texture (Renal glomeruli, Black arrows and renal proximal tubules, Red arrows). H&E stain, 10X. Source: Authors.

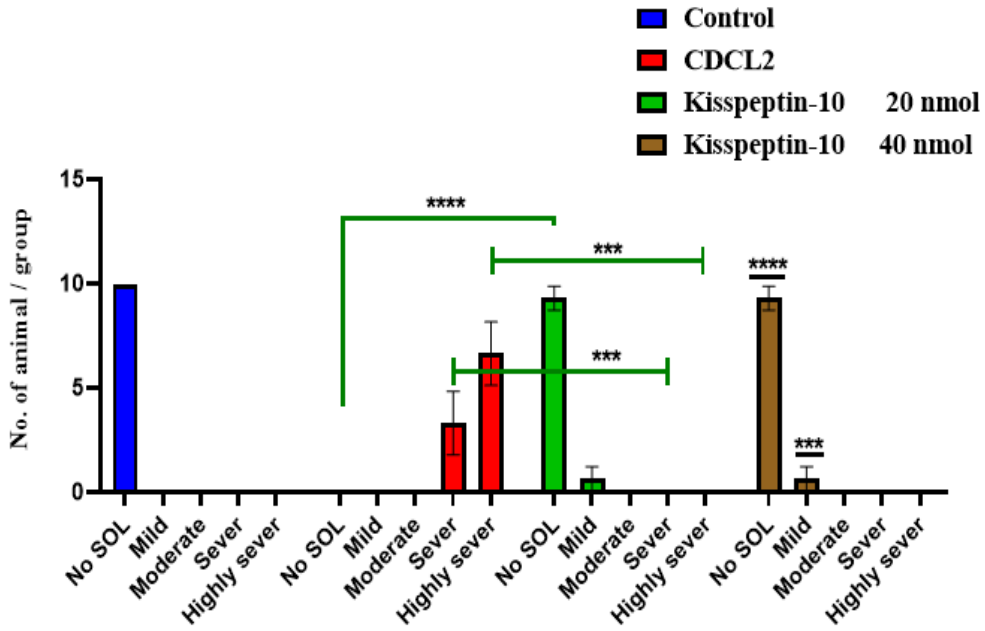

Figure 2 animal groups. The graph shows the different lesion grades in the rat tissues in four groups due to cadmium chloride intraperitoneal injection (1mg/kg B.W.) for two weeks and after that, the rats treated with Kisspeptine-10 every 72 hrs., for one-month intraperitoneal injection in both 20 and 40 nanomolar. The damage scores show a significantly decreasing after treatment with Kisspeptine-10 in both doses

compared with the cadmium chloride control group. Each bar in the graph represents 10 rats for each group and horizontal bars represent mean ±SD. Turkey's multiple comparisons One-way ANOVA was performed to calculate the significant differences. **** p ≤0.0001, *** p ≤ 0.001. Source: Authors.

Table 1. Histopathological scoring differences for splenic lesions in the rat in four experimental groups

Histopathological Score	Control		CDCL2		Kisspeptin-10 20 nanomolar		Kisspeptin-10 40 nanomolar	
	No.	%	No.	%	No.	%	No.	%
No SOL (0)	10	100	0	0	9	90	10	100
Mild (1)	0	0	0	0	1	10	0	0
Moderate (2)	0	0	0	0	0	0	0	0
Sever (3)	0	0	3	30	0	0	0	0
Highly Sever (4)	0	0	7	70	0	0	0	0
Total	10	100	10	100	10	100	0	0
Score	No SOL		Highly sever		NO SOL		NO SOL	

Source: Authors

Table 2. Histopathological scoring differences for hepatic lesions in the rat in four experimental groups

Histopathological Score	Control		CDCL2		Kisspeptin-10 20 nano molar		Kisspeptin-10 40 nano molar	
	No.	%	No.	%	No.	%	No.	%
No SOL (0)	10	100	0	0	10	100	9	90
Mild (1)	0	0	0	0	0	0	1	10
Moderate (2)	0	0	0	0	0	0	0	0
Sever (3)	0	0	5	50	0	0	0	0
Highly Sever (4)	0	0	5	50	0	0	0	0
Total	10	100	10	100	10	100	0	0
Score	No SOL		Sever / Highly sever		NO SOL		NO SOL	

Source: Authors.

Table 3. Histopathological scoring differences for renal lesions in the rat in four experimental groups

Histopathological Score	Control		CDCL2		Kisspeptin-10 20 nano molar		Kisspeptin-10 40 nano molar	
	No.	%	No.	%	No.	%	No.	%
No SOL (0)	10	100	0	0	9	90	9	90
Mild (1)	0	0	0	0	1	10	1	10
Moderate (2)	0	0	0	0	0	0	0	0
Sever (3)	0	0	2	20	0	0	0	0
Highly Sever (4)	0	0	8	80	0	0	0	0
Total	10	100	10	100	10	100	0	0
Score	No SOL		Highly sever		NO SOL		NO SOL	

Source: Authors.

Toxicity by cadmium chloride can induce oxidative stress *via* increasing reactive oxygen species (ROS), in living body organs. The toxicity leads to moreover injuries for vital cells and caused deleterious injury to tissues of the reproductive system and inducing male infertility. In cells, linking cadmium chlorideis to sulfhydryl (SH) groups can increase the peroxidation of lipids and interrupt fluidity and permeability (Valko *et al.*, 2016). In other words, when the cell membrane is damaged by free radicals, the cells are lost and thus the total cells are exposed to the risk. In this regard, the

production of ROS will be increased resulting in inducing of lipid peroxidation (Robin, 2013; Valko *et al.*, 2016).

Nowadays, kisspeptin has undoubtedly considered as one of the main proteins regulating not only the mechanisms underlying reproductive functions but also the neuronal networks that integrate sexual and emotional behavior with reproductive functions. Recently, most of the data are focused on the sexual role of kisspeptin in the central nervous system, so it will be of great interest in the next research to explore its role in some organ functions in healthy conditions as well as in the diseases (Melka *et al.*, 2021).

A previous study has reported that the kisspeptin signaling pathway is extensively involved in the regulation of endothelial cells, macrophages, monocytes, cardiomyocytes, and cells of the hypothalamus and extravillous trophoblast (Luque *et al.*, 2007*)*. Sato *et al*. (2017) proved the vital role of Kisspeptin in the regulation of inflammatory response against pathogens/toxins *via* KP/GPR54 signaling cascade that may serve as a potential therapeutic target for several diseases. Moreover, it has been demonstrated that kisspeptin positively regulated the gonadotropin-releasing hormone-expressing neurons (GnRH neurons), in which resulting in prevention postoperative adhesions, inflammation and fibrosis (smith *et al*., 2005; Lehman *et al*., 2013). McMillin *et al.* (2017) informed that GnRH played an important role in the activation of hepatic stellate cells during cholestatic liver disease. Kyritsi *et al.* (2017) established that targeting the GnRH / GnRHR1 signaling pathway may be a key to the management of hepatic fibrosis during the progression of primary sclerosing cholangitis. Furthermore, Kisspeptin via the Kiss1R gene can stimulate Gq/11- mediated pathway resulting in increasing intracellular Ca^{2+} and activating the extracellular signal-regulated kinase (ERK)-signaling pathway (Liu *et al*., 2008; Bianco and Kaiser, 2013).

4. Conclusion

This study aimed to examine the anti-toxic role of Kisspeptin in some vital organs including the liver, spleen, and kidney. Kisspeptin is demonstrated as a detoxification agent via the elimination of toxicity of cadmium chloride to some organs of living rats such as the liver, spleen, and kidney. Direct negative effects of Kisspeptin on these organs have only been recognized. The results indicate that the kisspeptin-10 has an active role as an anti-toxic effect due to cadmium chloride toxicity, and the data represent a promising path for the development of research into this problem.

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Conflict of interest:
The authors declare no conflict of interests.

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