AJMAS
https://journal.utripoli.edu.ly/index.php/Alqalam/index eISSN 2707-7179

Original article

Effects of Paracetamol on Submandibular Salivary Glands in Albino Rats

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ARTICLE INFO

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Received*: 20-05-2023*
Accepted*: 10-06-2023*
Published*: 14-06-2023*

Keywords*. Salivary, Apoptotic, Duct, Paracetamol, Rat.*

ABSTRACT

Background and aims*. Paracetamol (AAP) is the most common drug used as an analgesic and antipyretic. It can induce oxidative stress which can cause cell death. The aim of this study was to assess the effect of paracetamol on the submandibular salivary gland (SMG)of Albino rats.* ***Methods****. Twelve adult male albino rats were used, divided into control and experimental groups. The experimental group received orally 350mg/kg (paracetamol) once daily for 4 weeks and control groups received 2ml physiologic saline, and methyl cellos once orally daily during whole experimental period.* ***Results****. Histological examination of the experimental group showed that acinar cells demonstrated pyknotic and deeply stained nuclei with many cytoplasmic vacuolations. The ducts showed some signs of degeneration with loss of their normal cellular outlines. However, showed degenerative changes. Apoptotic changes expressed by anti-active caspase 3 were more obvious in acinar cells than in ductal cells. Statistical results showed a significant (P<0.05) statistical difference between the two groups.* ***Conclusion.*** *Long use of paracetamol leads to a degenerative and apoptotic change in acinar and ductal cells (SMG).*

Cite this article. *Daba A, Bogazia S. Effects of Paracetamol on Submandibular Salivary Glands in Albino Rats. Alq J Med App Sci. 2023;6(2):298-304. https://doi.org/10.5281/zenodo.8040551*

INTRODUCTION

A wide range of prescription medications contains AAP, which is freely accessible. Standard doses are often safe to use, but even a small overdose can be fatal. Compared to other over-the-counter medications, AAP is significantly more dangerous in overdose [1].

The analgesic impact of AAP is likely influenced by the rate and quantity of active medication that reaches the central nervous system, where its analgesic effect is felt [2,3]. The use of chronic AAP is common in illnesses such as toothaches, chronic backaches, chronic bone aches, and headaches that are connected to chronic pain [4,5]. AAP can also be physiologically addictive since the administered doses rise with each administration and are followed by the emergence of specific withdrawal syndromes such as headaches [6].

The US Food and Drug Administration estimates that 50 million adult Americans take AAP-containing products each week (FDA). When taken in therapeutic doses, AAP is considered to be safe, but at higher doses, it can result in centrilobular liver necrosis, which can be fatal. Acute liver failure is caused by acetaminophen intoxication around half of the time in the United States and Great Britain [7,8].

Centrilobular hepatic necrosis, steatosis, inflammatory cellular infiltrations, and fibrosis are the effects of AAP chronicity, and they can all persist for up to 1.5 years after the drug has been stopped being used. [9,10]. Even at therapeutic doses, AAP can alter the circulatory system, and long-term use of this medication has been linked to increases in blood pressure and the risk of hypertension, according to reports. However, little research has examined the

long-term effects of chronically ingesting therapeutic and supratherapeutic AAP dosages in humans and lab animals. [11].

AAP is also significantly secreted in saliva. It has been noted that in healthy patients, the correlation between plasma and salivary AAP concentrations is strong [12].

Additionally, the principle clinical symptoms of paracetamol overdose are nausea and vomiting within 2-3 hours of ingestion followed by abdominal pain in the right upper quadrant, liver dysfunction occurs within 24h and reached a maximum approximately 3-4 days after ingestion .The clinical and biochemical changes are a dramatic increase in serum Alanine Aminotransferase (ALT) and Asparatate Aminotrasferase (AST) levels, mild hyperbilirubinemia and increased in prothrombin , time saliva concentrations have been employed to examine the variations in AAP elimination following surgery [13] . Therefore, the current study attempted to assess the effect of AAP on the Submandibular salivary gland of Albino rats.

METHODS

Study design and experiments

In this study, twelve mature male albino rats were employed (weighing about 230-250 gm each). The ethics committee of the faculty of dentistry at Ain Shams University successfully applied for and was granted animal testing authorization. The animals were kept in wire-mesh cages with a controlled temperature and dark-light cycle. Bread, milk, and tap water were provided for the rats.

Paracetamol was obtained from AL Debeiky for Pharmaceutical Industries (AL-DebeikyPharma) in Cairo Egypt in the form of pure powder. Preparation of Paracetamol was done in physiologic saline and carboxyl methyl cellos. The required dose of 350mg/kg was, and each rat had administrated in 2ml from prepared drugs [14].

The animals were divided into two groups. The first group was the experimental group contains 6 rats that were given 350 mg/kg (paracetamol) orally once daily for 4 weeks [14]. The second group was served as a control group and consisted of 6 rats that were given 2ml physiologic saline and carboxyl methyl cellos orally, once daily for 4 weeks. At the end of the experiment, all animals were sacrificed by cervical dislocation for further analysis.

Samples collection and preparation

Hematoxylin and eosin (H&E) preparation: submandibular glands were removed from the sacrificed rat bodies and immediately fixed in a 10% formalin solution for 48 hours. To identify histological alterations, the specimens were carefully cleaned under running water, processed, and stained with hematoxylin and eosin [15], and stained with anti-active caspase 3 antibodies [16]. The positive results for anti-active caspase-3 immunoreaction were indicated by a brown coloration in the cytoplasm and nuclei of the acinar and ductal epithelial cells with different intensities.

Immunohistochemically Evaluation

Immunohistochemically Evaluation was done using Olympus CX 41 image analyzer computer system submandibular salivary glands were enclosed inside the standard measuring frame & then the immunological reaction for caspase 3 proteins was masked by a blue binary color to be measured. Seven immunoassays sections were used for measuring the caspase 3 area percent in each group. At least 20 measures were done in each section using a total magnification of x400.

Statistical analysis

Data were presented by the mean and standard deviation (SD), independent sample t-test was used to compare between groups and in comparison, between ducts and acinar reaction to caspase 3. The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM SPSS Statistics Version 20 for Windows.

RESULTS

Examination of the H&E-stained sections of rat (SMG) of the control group almost revealed the same normal histological picture of parenchymal elements (Fig.1).

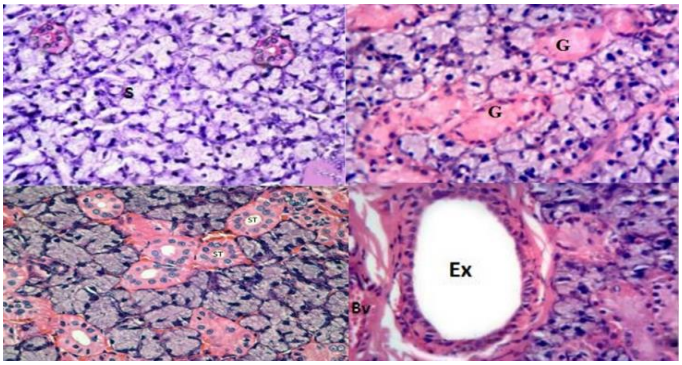

Figure 1. Photomicrograph of the SMG of the control group (H&E, org. mag. x400) showing(A) serous Acini (s) lined by pyramidal cells having basophilic cytoplasm and basally situated rounded nuclei. (B) GCTs (G) with basal rounded nuclei and many apical eosinophilic granules (C)striated ducts (ST) were lined by columnar cells with centrally placed nuclei and eosinophilic cytoplasm with basal striations. (D)excretory duct (Ex) lined by pseudostratified columnar epithelium with an empty lumen surrounded by fibrous C.T. and a neighboring blood vessel (BV).

However, examining the H&E-stained sections of the experimental group (administered AAP for 4 weeks) revealed serous acini with ill-defined outlines. Most of the acinar cell's nuclei appeared deeply stained with irregular shapes. Some nuclei appeared pyknotic, while others were observed crescent in shape. The acinar cell cytoplasm appeared faint basophilic staining. Some cytoplasmic vacuolations were observed in some cells, and areas of degeneration were observed represented with cellular remains (fig 2A).

The granular convoluted tubule (GCTs) showed ill-defined cell outlines, with apparently reduced apical eosinophilic granules. Few cells showed cytoplasmic vacuoles. Extravasated RBCs were observed between acini in some specimens (fig 2B). The striated ducts appeared also with ill-defined cellular outlines and loss of basal striations. Most of their cells showed cytoplasmic vacuolations and neighboring BVs appeared with a thickened wall (fig 2C). The excretory duct showed a loss of pseudo-stratification. The cells were relatively reduced in height, and some areas showed signs of degeneration and vacuolations. The duct appeared with an empty lumen and was surrounded by thick fibrous connective tissue (CT) and the walls of neighboring blood vessels (BVs) were relatively thickened (fig 2D). In other specimens, the BVs were dilated &engorged with RBCs (fig 2E).

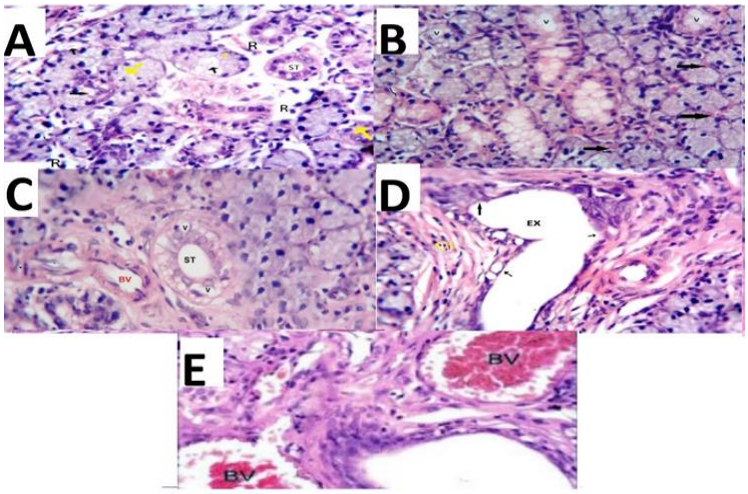

Figure 2. photomicrograph of SMG from subgroup (H&E, org. mag. x400) showing (A) ill-defined serous acinar shape. Most of the nuclei appeared deeply stained & pyknotic. Some nuclei appeared crescent (yellow arrow), and cells with cytoplasmic vacuolation (black arrow). Areas of degeneration represented by cellular (B) GCT with ill-defined cell outlines reduced apical eosinophilic granules. Few cells showed cytoplasmic vacuolation (v). Few extravasated RBCs were observed between acini (arrows). (C) striated duct (ST) with ill-defined cellular outlines, and loss of basal striations. Most of their cells showed cytoplasmic vacuolations(v) and neighboring BV appeared with thickened walls. (D) excretory duct with loss of pseudo stratification of lining cells some cells showed signs of degeneration& vacuolations (black arrow), thick fibrous CT surrounding the duct which appeared with an empty lumen. (E) excretory duct neighbored with dilated BVs engorged with RBCs.

Immunohistochemical staining of submandibular salivary gland sections of the control group showed an almost negative staining reaction in both acinar and ductal cells. Few acinar cells showed mild positive cytoplasmic staining reaction to anti-active caspase 3 (Fig 3A). Similarly, most of the ducts were negatively stained, and some cells with a mild positive reaction to anti-active caspase 3 (Fig 3B).
Examination of the immunohistochemically stained sections of SMGs of the Experimental group revealed wide areas of positive stained reaction of acinar cells to anti-active caspase 3 (Fig 3C). While concerning the ductal system their lining cells showed mild to moderate positive staining reaction to anti-active caspase 3(Figure 3D).

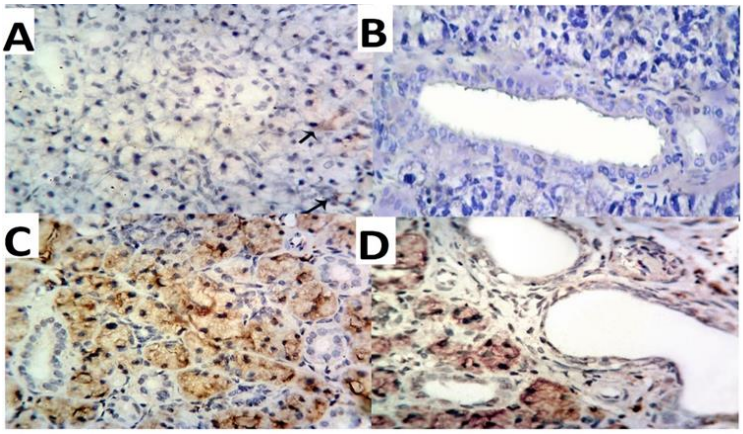

Figure 3. An photomicrograph of the control group (Anti-active caspase 3 org. mag. x400). Showing (A) negative stained reactions in both acinar and ductal cells. Few acinar cells showed mild positive cytoplasmic stained reaction to anti-active caspase 3 (arrows). (B) excretory duct showing negative to anti-active caspase 3 & few with a mild positive reaction. (C) large areas of positive stained acinar cells to anti-active caspase 3, mildly stained ducts. (D)mild to moderate staining of the excretory duct of lining cells

Regarding caspase 3 area percentage in the acini, there was a statistically significant difference between the studied two groups (P = 0.001), and experimental group showed highest value (table 1). While, caspase 3 area percentage in the ducts, there was a statistically significant difference between the studied two groups (P = 0.001) and the experimental group showed highest value (table 1).

Table 1. Descriptive statistics, comparison between Caspase 3 area percent in submandibular salivary glands acini of the control and experimental groups (independent sample test)

Group	Mean	S. deviation	P
Acini			0.001
Control groups	0.788	0.7908	
Experimental	18.978	8.2988	
Ducts			0.001
Control	0.18	0.30295	
Experimental	1.395	0.6463	

$P \leq 0.05$ is considered significant.

On comparing caspase 3 area percentages between acini and ducts, the acinar cells showed higher values compared to ductal cells. Where independent sample test showed significant differences between them for control and experimental groups respectively (figure 4 & table 2).

Table 2. Descriptive statistics, comparison between Caspase 3 area percent in submandibular salivary glands acini and ducts of the two groups

Group	Acini		Ducts		P
	Mean	S.deviation	Mean	S.deviation	
Control	0.788	0.97087	0.18	0.30295	P=0.011
Experimental	18.978	8.29884	1.395	0.64634	P<0.001

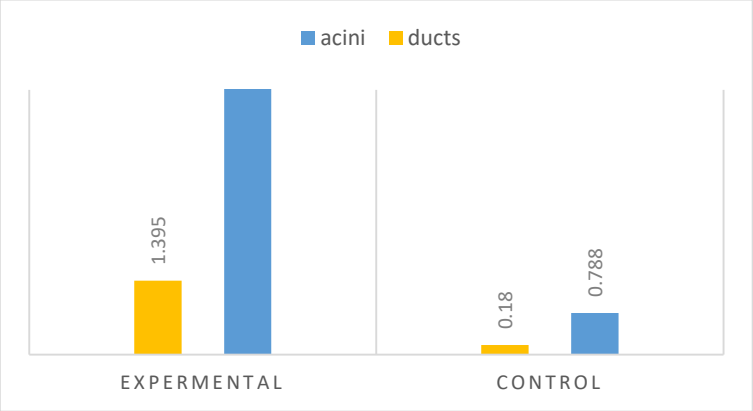

Figure 4. Bar chart representing mean Caspase 3 area % in Submandibular salivary glands acini and ducts of the two groups

DISCUSSION

The results of the current study's H&E staining of experimental group 1 (which received AAP) revealed ill-defined acinar and ductal cell outlines. Our study results are consistence with a previous study where administering rats a single dose of 500 mg/kg AAP induced glomerular injury as seen by the loss of cellular outlines [17]. Also other previous study explained that faint basophilia is caused by degenerative changes, such as a reduction in the amount of rough endoplasmic reticulum and the removal of mitochondrial cristae in rat hepatocytes. The acinar cells in the experimental group of our study also revealed a weak basophilic stain in their cytoplasm. A previous study reported hyperchromatic nuclei in liver cells after giving mice 300 mg/kg of AAP intraperitoneally, and our finding is consistent with their findings [18].

Our results were also in line with a study that found many pyknotic nuclei in rat hepatocytes after an intraperitoneal injection of 1000 mg/kg AAP, showing that the liver cells' protein structure had deteriorated [19]. Moreover, the current study supported the findings of earlier research that proposed that the vacuolation of the cytoplasm of the acinar and ductal cells was caused by an accumulation of lipid droplets from wasted fatty acids as a result of decreased cellular activity [20]. This was also described as lipid build up because of either an increase in lipid uptake by the cells for use as an energy source or a decrease in its utilization in the formation of secretory granules and plasma membranes. Nevertheless, could come from the loss of secretory granules and their replacement with vacuolar structures in the serous acini. These findings were reported by researchers [21] who found vacuoles scattered throughout the kidney cells of rats given an intraperitoneal dosage of 1000 mg/kg AAP. In addition, another study reported that rats' kidneys and livers showed signs of cytoplasmic vacuoles after consuming 1g/kg AAP for 14 days. This study showed several acinar cell gaps and cellular remains, which may suggest that these were signs of degeneration [22].

The GCTs in the current study's experimental group exhibited a variety of degenerative changes and cytoplasmic vacuoles. One study found that rats who received a single intraperitoneal injection of 1000 mg/kg AAP had kidney vacuoles that were disseminated throughout the cytoplasm, a loss of border outline, and protein casts in the lumen of the proximal and distal convoluted tubules. The pharmaceutical toxicity brought on by AAP may have produced a decline in epidermal growth factor (EGF) levels, which could be the reason for this. These changes suggested adverse effects of AAP on the kidney [21], which may influence SMG [23]. Furthermore, in this experimental group, cellular degenerations and loss of basal striations were visible. This may be explained by a study that suggested that the liver cells affected by AAP revealed mitochondrial disruption and damage, which would be attributed to the accumulation of Ca2+, which in turn limits mitochondrial ATPase function and lowers energy generation. The mitochondrial membrane rupture and release of cytochrome c that results from increased mitochondrial Ca2+ release promote apoptotic cell death [24]. The present study striated ducts and basal striations would have been damaged by the mitochondrial affection, similar to another study that demonstrated that degeneration occurs in mice after receiving a single dose of 1000 mg/kg intraperitoneal [25].

In this research, it was found that certain BVs in the experimental group had dilated, RBC-filled lumens and some RBCs were extravasated in between the acini (figure 2D and E). More BVs showed signs of slightly thicker walls because of the blood vessel wall impairment. This is consistent with a study's findings, which involved giving pregnant rats 7.3 mg/kg of AAP over 10 days orally. The researchers found that the rats' kidneys bled and their blood vessels congested [26]. Moreover, another study noted that oral treatment of 2.5 g/kg AAP to rats frequently resulted in vascular pathological alterations, kidney BVs was significantly thickened, and RBC extravasation was also observed as a symptom [27].

The current study found that the amount of fibrous connective tissue surrounding the excretory duct increased relatively, which may be related to a disruption in fibroblasts' remodeling activity. This is in line with earlier research that found that feeding mice a single dosage of 400 mg/kg AAP via stomach tube led to a considerably increased amount of fibrous tissue, which leads to liver fibrosis [10]. This outcome was in line with the findings of a different study, which showed that taking 750mg/kg of AAP orally for four weeks caused thickening of the CT surrounding the glomerular capillary in the kidney, adjustments to the density of mesenchyme, atrophy, and degeneration, and an expansion of Bowman's space [28]. In the current study, vacuolation among the epithelial lining cells and areas of degeneration was seen in the excretory duct epithelium of the SMG experimental group. In addition, cell size was reduced, and pseudo-stratification was lost. This result is in line with a prior study's observation that kidney epithelial lining deteriorated after receiving a single dosage of 2.5 g/kg of AAP through a stomach tube.
It was hypothesized that the epithelial cells had lost contact with the underlying matrix, which would have caused cell death, shedding, and loss of pseudo-stratification [29]. This finding supports a previous study's notion that mice given 400 mg/kg AAP intraperitoneally experienced significant LNG-related ductal cell death as evidenced by the widespread development of degeneration, pale, shrinking, and flattened duct cells [29].

CONCLUSION

Acetaminophen caused various histological and apoptotic changes in acinar and ductal cells of submandibular salivary glands. The apoptotic changes which expressed by Anti-active caspase 3 were more obvious in acinar cells than in ductal cells.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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آثار الباراسيتامول على الغدد اللعابية تحت الفك السفلي في الجرذان البيضاء

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الملخص

الخلفية والأهداف. الباراسيتامول (AAP) هو أكثر الأدوية شيوعًا المستخدمة كمسكن وخافض للحرارة. يمكن أن يسبب الإجهاد التأكسدي الذي يمكن أن يسبب موت الخلايا. كان الهدف من هذه الدراسة هو تقييم تأثير الباراسيتامول على الغدة اللعابية تحت الفك السفلي (SMG) في الجرذان البيضاء. **طُرق الدراسة**. تم استخدام اثنا عشر ذكور جرذ ألبينو بالغة مقسمة إلى مجموعة ضابطة ومجموعتين تجريبية. تلقت المجموعة التجريبية 350 ملجم / كجم (باراسيتامول) عن طريق الفم مرة واحدة يوميًا لمدة 4 أسابيع ، وتلقت المجموعة الضابطة 2 مل من محلول ملحي فيزيولوجي ، وتشيلو الميثيل مرة واحدة يوميًا خلال فترة التجربة بأكملها. **نتائج الدراسة**. أظهر الفحص النسيجي للمجموعة التجريبية أن الخلايا الأسينار أظهرت نوى متخمرة وملطخة بعمق مع العديد من الفجوات السيتوبلازمية. أظهرت القنوات بعض علامات الانحطاط مع فقدان الخطوط العريضة الخلوية الطبيعية. ومع ذلك ، أظهرت تغيرات تنكسية. كانت التغييرات المبرمجة التي تم التعبير عنها بواسطة كاسباس 3 المضاد للنشاط أكثر وضوحًا في الخلايا الأسينار منها في الخلايا الأقنية. أظهرت النتائج الإحصائية وجود فروق ذات دلالة إحصائية ($P < 0.05$) بين المجموعتين. **الخاتمة**. يؤدي الاستخدام المطول للباراسيتامول إلى تغير تنكسي وموت الخلايا المبرمج في الخلايا الأقنية والأسينار.(SMG)

مفاتيح الكلمات: اللعاب ، التنخر ، مجرى الهواء ، باراسيتامول ، الفئران