

Paracetamol Overdose Induces Physiological and Pathological Aberrations in Rat Brain

Amina E. Essawy¹, Afrah F. Alkhuriji², Ahmed A. Soffar^{1*}

¹Department of Zoology, Faculty of Science, Alexandria University, Alexandria, Egypt.

²Department of Zoology, College of Science, King Saud University, Saudi Arabia.

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ABSTRACT

Paracetamol (Acetaminophen) is one of the most popular over the counter medications that is commonly used as an anti-inflammatory and pain killer, and to relieve fever and headaches. Despite its several therapeutic benefits, it is well known that an overdose of paracetamol can lead to hepatic and renal damage. Considering that brain cells is one of the main targets for paracetamol in the body, the effect of paracetamol on the physiology and histology of the brain is been poorly investigated. Hence, the present work investigates the possible adverse effects of paracetamol on the rat brain. Our results show that an overdose treatment of paracetamol caused significant elevation in the activity of AChE and a remarkable suppression in levels of dopamine and serotonin in treated rats. Also, applying rapid Golgi-cox staining showed that paracetamol induced morphological aberrations and a dramatic reduction in the density of dendritic spines in brain cells. Histological and ultrastructure alterations were also recorded in the neurons of paracetamol-treated rats. In conclusion, we found that an overdose of paracetamol is neurotoxic. The observed alterations point to the possibilities of higher brain impairments which is of strong public health concern.

INTRODUCTION

Paracetamol (Acetaminophen, N-Acetyl-p-Aminophenol) is widely used as prescription and over the counter (OTC) analgesic and antipyretic agent (Trumper *et al.*, 2005). A major problem is the misuse of paracetamol through intentional or unintentional uptake of suprathreshold doses, which may lead to hepatic and renal adverse side effects in humans and experimental animals (Guo and Nzerue 2002; Toklu *et al.*, 2006). Paracetamol is metabolized mainly in the liver via conjugation with glucuronic acid and sulphate, and finally excreted in urine. Paracetamol metabolism also yields a cytochrome P450-dependent highly reactive metabolite known as

N-acetyl-p-benzoquinonimine (NAPQI). This metabolite is able to react with glutathione (GSH) forming a non-toxic conjugate to be excreted via kidneys (Henderson *et al.*, 2000; Manyike *et al.*, 2000; Walubo *et al.*, 2004). Critically, overdoses of paracetamol saturates these neutralization metabolic pathways thus the rate of formation of NAPQI exceeds the capacity to detoxification. The excess NAPQI binds to cellular proteins, including mitochondrial proteins, leading to an oxidative stress-mediated liver damage (Henderson *et al.*, 2000; Ojo *et al.*, 2006). Importantly, Cytochrome P450 isoform CYP2E1 is also expressed in the brain, suggesting that paracetamol might be metabolized by nerve cells producing the toxic metabolite NAPQI (Joshi and Tyndale 2006). Also, considering its feasibility to crosses the blood brain barrier, a high dose of paracetamol may lead to NAPQI-mediated adverse neurotoxic effects (Fischer *et al.*, 1981). Despite intensive investigations of the toxic effect on liver and kidney tissues, information about pathological effects of paracetamol on the neuronal tissue is relatively rare.

* Corresponding Author

Ahmed Soffar, Department of Zoology, Faculty of Science, Alexandria University, Alexandria, Egypt. Email: ahmedsoffar@gmail.com

Hence, the purpose of this work is to clarify the effect of paracetamol overdose on nerve tissues. We investigated the effect of paracetamol on the physiological activity of Acetylcholinesterase (AChE) and monoamines (dopamine and serotonin). Importantly, we coupled our physiological study with an intensive investigation for the anatomical as well as the cellular and subcellular changes in the brain tissue in response to paracetamol treatment.

MATERIALS AND METHODS

Experimental animals

A total of 16 adult male Wistar albino rats, of 150-160 g body weight, were used in this study. Animals were housed in standard metallic cages (4 rats per cage) and kept in a temperature-controlled environment (22 ± 2 °C) with an alternating 12 h light-dark cycle. Rats were acclimatized to the lab environment for 1 week prior to the experiment. The animals had free access to commercial food pellets and clean drinking water. The experiments were done in compliance with the Guide for the Care and Use of Laboratory Animals.

Chemicals used

Paracetamol (Panadol 665, GlaxoSmithKline Australia Pty Limited, Australia) was obtained from a local medical store (Alexandria, Egypt). Kits for the measurement of serum AChE were purchased from Span Diagnostics Ltd. (Surat, India). Dopamine and serotonin ELISA measurement kits were purchased from GenWay Biotech Inc. (San Diego, CA, USA) and DLD-Gesellschaft für Diagnostika und medizinische Geräte mbH (Hamburg, Germany) respectively.

Experimental design

Animals were randomly divided into 2 groups of 8 rats each. Group 1: Animals were orally given distilled water (2 ml) for 15 days and served as controls. Group 2: Animals were orally given paracetamol (650 mg/kg b.wt. dissolved in 2 ml distilled water (Yousef *et al.*, 2010)) daily for 15 days. Blood samples were collected from both control and experimental animals as described in (Khayyat *et al.*, 2017), then animals were sacrificed and brains were quickly removed and prepared for neuroanatomical, histological and ultrastructural studies as described below.

Measurement of neurochemicals

We measured the Acetylcholinesterase activity in the serum of animals. Briefly, serum was separated out from blood samples by centrifugation at 3000 rpm for 10 min. AChE activity was determined in plasma using acetylcholine iodide as a substrate as described in (Ellman *et al.*, 1961). In this method, AChE in samples hydrolyzes acetylthiocholine iodide into thiocholine and butyric acid. The thiocholine reacts with 5,5'-dithiobis-2-nitrobenzoic acid to form 5-thio-2-nitrobenzoic acid. The developed yellow color is measured spectrophotometrically. Dopamine and serotonin levels were measured in the brain tissue

of control and paracetamol-treated animals according to manufacturer's protocols. All measurements were carried out using Elico-SL177 spectrophotometer (Elico LTD. Hyderabad Andra Pradesh, India).

Neuroanatomical study

For detection of the morphological changes in perikarya, dendrites and axons, rapid Golgi-cox staining technique was used (Shankaranarayana Rao *et al.*, 2001). Animals from control and paracetamol-treated groups were deeply anesthetized with diethyl ether. Brains were carefully removed from skulls and immersed en-block in rapid Golgi solution in colored bottles for 1 day and replaced with fresh fixative. The composition of Golgi solution was: 5% potassium dichromate, 5% chloral hydrate, 4% glutaraldehyde, 2.5% formaldehyde, 0.5% DMSO (Adermark and Lovinger 2006). One day later, the fixative in which the tissue was immersed on day 1 was slowly poured out. The tissue was rinsed for 2 days by adding a small amount of fresh fixative and kept in the dark chamber every 24 h. The tissue blocks remained undisturbed in the fixative for another 24 h and then were rinsed for 4 days in 0.75% aqueous solution of silver nitrate (AgNO_3) till the reddish-brown color of the potassium dichromate-silver complex disappeared.

Tissue pieces were placed in a petri dish and silver deposits were gently brushed off. After dehydration, the tissue blocks were carefully mounted onto block holders with required orientation and embedded with paraffin wax. The brain tissue was cut into 100 μm thick sections in horizontal plane. The sections were collected in a Petri dish containing 100% alcohol and transferred to xylene for clearing and finally were mounted serially on slides with DPX. Slides images were captured using an Olympus Fluorescent Microscope imaging system.

Histological and Ultrastructural studies

For histopathological study, brains of control and paracetamol-treated animals were dissected out and fixed in 10% formalin for 24 h. Washing was done by rinsing the sample in tap water for 24 h. Sample dehydration was performed using serial dilutions of ethanol. Specimens were cleared in xylene and embedded in paraffin. Paraffin sections (5 μm) were stained by hematoxylin and eosin according to (Bancroft *et al.*, 1996) for histopathological examination.

For ultrastructural examination, small pieces of brain were immediately immersed in 4FIG in phosphate buffer (pH 7.2) fixation mixture for 3 h at 4 °C then post-fixed in 2% OsO_4 (Osmium tetroxide) at 4 °C for 2 h. The specimens were dehydrated in graded series of ethanol then embedded in Epon-araldite mixture in labeled beam capsules. LKB ultramicrotome was used to obtain ultrathin sections (50 nm thick) which were picked upon 200 mesh naked copper grids. Grids were double stained with uranyl acetate for ½ h and lead citrate for 20-30 min. Scoping the grids was achieved by using Jeol 100CX Transmission electron microscope (TEM).

Statistical Analysis

The results were expressed as mean \pm SD were analyzed by Student's *t*-test using Microsoft excel® 2016. Values of *p* < 0.05 were considered to be statistically significant.

RESULTS

Paracetamol treatment alters the activity of Acetylcholinesterase and levels of monoamines

The activity of AChE in plasma of control and paracetamol-treated rats are shown in Figure (1a). Interestingly, we found a significant (*p* < 0.05) 3-fold increase in the level of AChE activity in paracetamol-treated rats as compared to control rats (174.7 ± 58.8 & 53 ± 12.5 unit/L respectively). On the other hand, levels of the two key player neurotransmitters within the brain tissue, dopamine and serotonin, were suppressed to more or less half their original levels as compared to controls (Figs. 1b, c).

Morphological aberrations of dendrites and dendritic spines after paracetamol treatment

In this work, we applied Golgi-cox staining to brain section to reveal detailed morphological architecture of neurons. The neuronal cell bodies together with their projections are stained dark brown in the after impregnated by Golgi-cox stain. Brain sections of control rats are represented by figures 2a and b. In controls, perikarya appear polygonal or oval. Neuronal spines are well recognizable and appeared as membranous protrusions arising from the neuronal surface of dendrites. Brain sections of paracetamol-treated animals show morphological abnormalities including a clear initial degeneration of neuronal axons (Fig. 2c).

Moreover, we observed a dramatic reduction in the density of the dendritic spines in brain sections from animals treated with paracetamol as compared to controls (Fig. 2d).

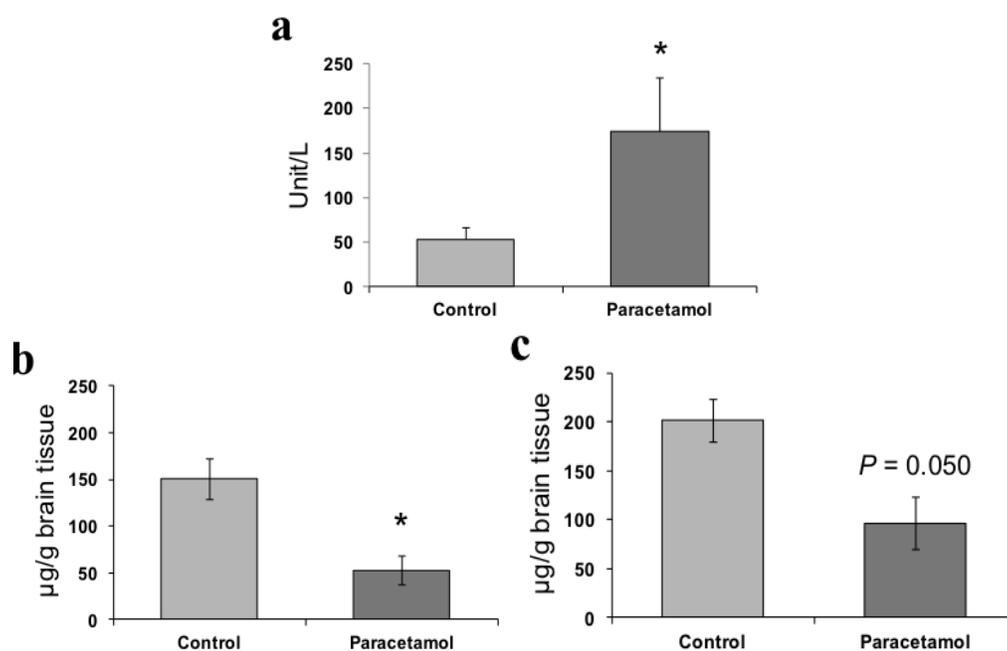


Fig. 1: Neurochemical analysis of AChE activity and dopamine, and serotonin levels after Paracetamol administration. (a) Serum levels of AChE activity in control- and Paracetamol-treated rats. Values are mean \pm SD for three rats in each group. **p* < 0.05. (b) Brain tissue levels of dopamine in control- and Paracetamol-treated rats. (c) Brain tissue levels of serotonin in control- and Paracetamol-treated rats. Values are mean \pm SD for three rats in each group. **p* < 0.05.

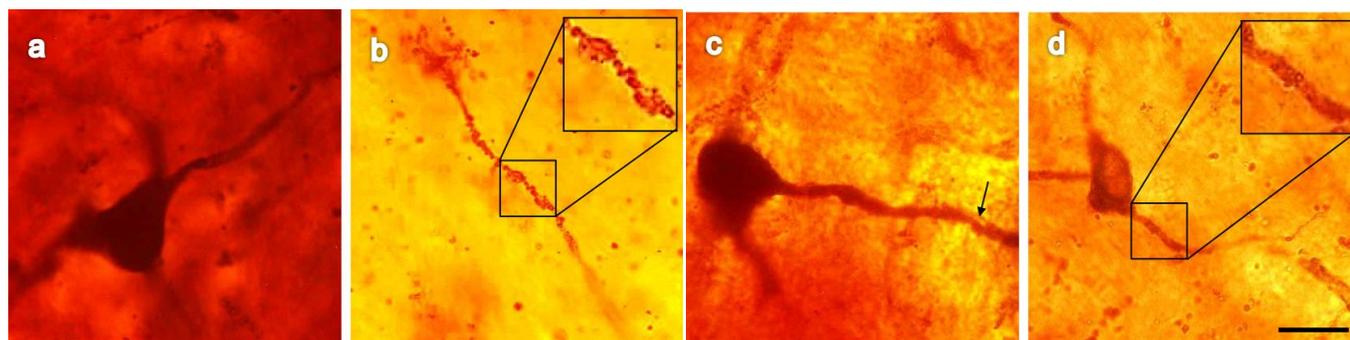


Fig. 2: Light micrographs of cortical neurons from control and Paracetamol-treated rats (Golgi-cox stain). (a) A control neuron from control rat with normal architecture of perikaryon, axon and dendrites. (b) A typical dendron of a neuron of control rat carrying many dendritic spines (enlarged part). (c) A neuron from Paracetamol-treated rat showing degenerated parts a long its axon (arrow). (d) A dendron from Paracetamol-treated rat showing dramatic reduction in spine number as compared with control neurons. (a - d), Scale bar, 10 μ m; enlarged parts, 5 μ m.

Paracetamol induces histopathological and ultrastructural alterations in brain tissue

Normal histological architecture of the brain tissue was shown in brain sections from control rats (Fig. 3a). Paracetamol treatment induced several histopathological alterations in both neurons and neuroglia cells of brain tissue. Several neurons showed signs of degeneration, including cytolysis and chromatolysis (Fig. 3b). Spongiform necrosis and nuclear pyknosis were observed (Fig. 3b). Also, we observed degenerated neuroglia containing pyknotic nuclei and congested cerebral blood vessels with detached endothelial wall in paracetamol-treated animals (Fig. 3c). Electron micrographs of brain cortex of untreated rats

showed normal neuronal soma and normal neuropile with myelinated and unmyelinated nerve fibers containing normal mitochondria and normal light and electron dense synaptic vesicles (Figs. 4a & b). Normal protoplasmic glial cells were also seen (Fig. 4a).

Degenerated neurons with complete lyses of cytoplasm, irregularly shaped nuclei, dilated and disorganized cisternae of rough endoplasmic reticulum, damaged mitochondria and ruptured synaptic vesicles were observed in brain of animals treated with paracetamol (Figs. 4c-e). The cytoplasm of some glial cells appeared electron dense, with altered mitochondria and disorganization of the inner membrane system.

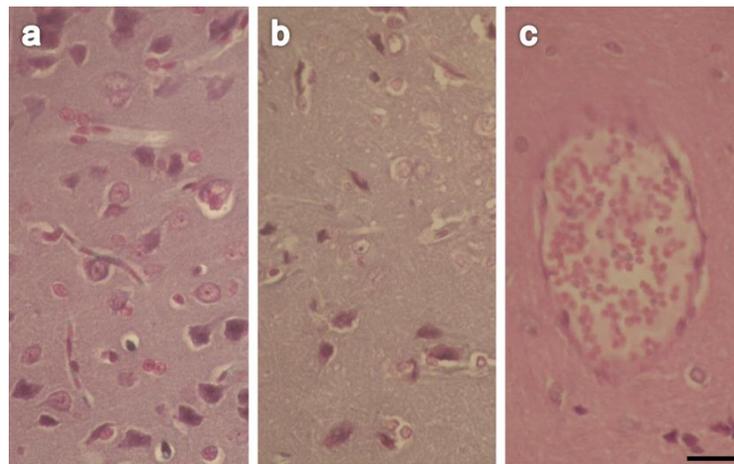


Fig. 3: Light micrographs showing histological changes in the brain of rat after treatment with Paracetamol. (a) A group of cortical neurons of control rat with large globular or ovoid nuclei surrounded by a small amount of cytoplasm. (b) A group of neurons of Paracetamol-treated rat showing signs of degeneration including cytolysis and chromatolysis. (c) Cerebral congested, dilated blood vessel in Paracetamol-treated rat with detached endothelial wall. Scale bar, 20 µm.

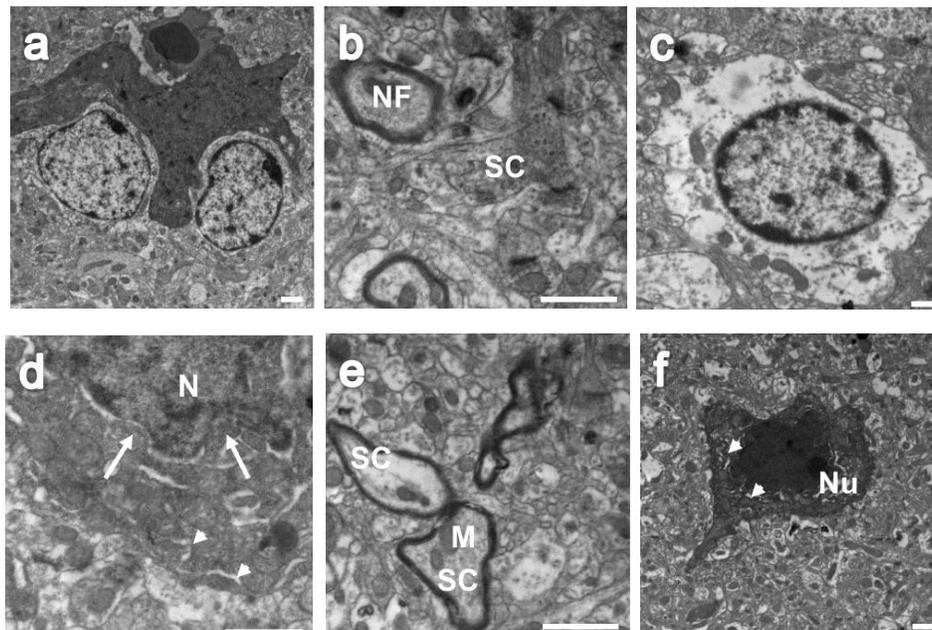


Fig. 4: Electron micrographs showing parts of the cerebral cortex of control (a, b) and Paracetamol-treated rats (c - f). (a) Two neurons and their serving microglia cell (MC). (b) Myelinated nerve fiber (NF) with synaptic vesicles (SV). (c) A neuron with complete lysis of the cytoplasm and damaged cytoplasmic organelle. (d) Enlarged part of a neuron, showing irregular-shaped nucleus (N) with indentation and dilation of the nuclear envelope (arrows). Note also: cytoplasm containing dilated and disorganized cisternae of endoplasmic reticulum (arrowheads). (e) Nerve fibers (NF) containing degenerated synaptic vesicles and damaged mitochondria (M). (f) A glial cell with abnormal outline and electron dense nucleus possessing severe indentation of nuclear envelope and peripherally located nucleolus (Nu). Arrowheads indicate fragments of dilated rough endoplasmic reticulum. Scale bar, 500 nm.

DISCUSSION

In this study, we found that application of an overdose of paracetamol significantly elevated the plasma level of AChE in treated animals. It also produced several morphological, histological and ultrastructure aberrations thus indicating a possible brain injury. A recent study reported that an overdose treatment of paracetamol caused a significant increase in malondialdehyde (MDA) that is associated with a remarkable decrease of total antioxidant capacity in the brain of male albino rats (Mohammed and Safwat 2013). Moreover, the elevated level of MDA in the brain following a high paracetamol dose correlates with an increased rate of lipid peroxidation which is one of the main manifestations of oxidative damage (Sener *et al.*, 2003). The elevated AChE activity could be attributed to neuronal membrane damage due to increased lipid peroxidation (Kaizer *et al.*, 2005). Importantly, the increased AChE activity following administration of high doses of paracetamol will positively reduce the cholinergic neurotransmission efficiency by decreasing the level of acetylcholine in the synaptic cleft, but, on the other hand, may lead to an oxidative stress-mediated structural alteration in neurons.

Our study showed also that administration of high doses of paracetamol induced a significant depletion in dopamine and serotonin content in brain tissue. A recent study demonstrated a significant effect of the long term paracetamol treatment on the level of amino acids in different regions of the rat brain (Blecharz-Klin *et al.*, 2014). They reported that, the abnormal variability in various amino acids concentrations may be attributed to a wide range of pharmacological effects of paracetamol in the central nervous system. Also, the damage of neurons and the depletion of neurotransmitter level could be attributed to paracetamol-induced oxidative stress. A recent work showed that paracetamol administration caused a significant elevation in levels of thiobarbituric acid reactive substances (TBARS) and dichlorofluorescein oxidation in brain homogenate (da Silva *et al.*, 2012). Also, mitochondrial swelling and reactive oxygen species production increased after administration of paracetamol. Considering their important functions as neurotransmitters, the observed paracetamol-associated reduction in levels of dopamine and serotonin may critically lead to behavioral and emotional adverse side effects.

In the present work, our neuroanatomical study using rapid Golgi-cox staining technique revealed a dramatic reduction in the number of neural spines upon paracetamol treatment. Dendritic spines contain several essential compartments for synaptic function and plasticity such as neurotransmitter receptors, organelles, and signaling systems (Cheng *et al.*, 2010; Nimchinsky *et al.*, 2002). Defect in morphology or alterations in density of neural spines is associated with a growing number of human disorders (Lai *et al.*, 2016). A link between abnormal neural spines and mental retardation was suggested for first time by (Purpura 1974). Also, mental disorders such as schizophrenia is associated with decreased density of dendritic spines in neocortical pyramidal neurons (Garey *et al.*, 1998). In addition, patients with Down

syndrome have a decreased spine density in neocortex (Takashima *et al.*, 1989) and hippocampus (Ferrer and Gullotta 1990). On the contrary, a low dose of paracetamol may protect cerebral cortical neurons from oxidative stress and limits neuronal inflammation by reducing menadione-mediated oxidative neurotoxicity (Bisaglia *et al.*, 2002; Tripathy and Grammas 2009).

Our histological and ultrastructure investigation revealed different degenerative changes in brain cells in response to paracetamol treatment. These results coincide with the findings of (Posadas *et al.*, 2010) who reported a deleterious effect of paracetamol on cortical neurons, both *in vivo* and *in vitro*. In addition, paracetamol induces neuronal damage in cerebral granular cells (Mohamed *et al.*, 2014). Also, paracetamol is able to activate the neuronal CYP2E1 thus generating toxic metabolites such as NAPQI. The formation of NAPQI metabolite decreases glutathione levels leading to oxidative stress and neurotoxicity (Joshi and Tyndale 2006). Also, (Nencini *et al.*, 2007) reported that, an overdose of paracetamol decreases the levels of anti-oxidative stress candidates such as glutathione, ascorbic acid and is associated with a remarkable decrease in superoxide dismutase activity. Importantly, excessive production of reactive oxygen species in brain and the disturbance in balance between oxidative species antioxidant defenses are associated to pathological changes in neurodegenerative diseases (Halliwell 2006).

CONCLUSION

In conclusion, the results of this study point to the fact that administration of an overdose of paracetamol is neurotoxic. The remarkable degenerative changes upon Paracetamol administration in brain tissue of rats may be attributed to excessive oxidative stress. Future studies are necessary to clarify the exact neurotoxic mechanism of paracetamol in case of being used at high doses.

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