Biochemical Effect Of Melatonin Administration On Oxidative Stress Caused By Aging In Male Rats

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ABSTRACT

Nowadays, early aging represents a big problem among people due to physical and psychic strains together with industrial and environmental impurities. The present study was undertaken to elucidate the effect of aging as well as the possible effect of melatonin administration on the oxidative stress caused by aging. Cu/Zn superoxide dismutase (Cu/Zn SOD), glutathione peroxidase (GSH_{PX}) and Catalase (Cat) activities in addition to reduced glutathione (GSH) concentration and lipid peroxidation (malondialdehyde) level were determined in the heart , lung and kidney of all rats groups. Our results revealed that, aging induce significant decrease in the heart, lung and kidney Cu/Zn SOD, GSH_{PX} as well as cardiac catalase activities when compared with young control group. While melatonin returned their level near to the level of control young rats. Melatonin also reversed the reduction in cardiac and renal GSH concentration caused by aging. Malondialdehyde (MDA) level in the heart, lung and kidney tissues of aged male rats showed significant increase when compared with young control group. Melatonin ameleorate MDA level near to that of control young rats. These results were confirmed by histological examination which revealed myocardial changes, destruction of the alveoli in the lung and degranulation and desquamation of the renal tubules epithelium of the kidney of aged group. These histological changes were alleviated in the melatonin administrated group. We concluded that melatonin could be successfully used in reduction of oxidative stress caused by aging in the heart, lung and kidney tissues of male rat.

INTRODUCTION

Aging is a complex physiological phenomenon accompanied with various alterations in cellular component as antioxidant defense enzymes, which has a vital role in protecting tissues from oxidative damage. Different theories have been elaborated about its origin, among such theories, the free radical theory of aging which suggests that, free radicals influence the primary and several secondary age-associated aging processes such as decline of immune function, atherosclerosis, heart diseases and a shift in the prooxidant / antioxidant balance, that leads to increased oxidative stress, and dysregulation of cellular function, *(1)*. Moreover, the mitochondial respiratory chain is a powerful source of reactive oxygen species (ROS), which considered the causes of many diseases and aging *(2)*. A corollary of this theory is administration of molecules that, either prevent the formation of radicals or neutralize them once they are formed, that would change the rate of aging and reduce the incidence of age - associated diseases. *(3)*. One newly discovered agent that has the ability to protect against free radical-related processes is N-acetyl-5-methoxytryptamine, (melatonin). It plays an important role as an immune stimulant, and in treatment of depression, stress, and cancer. There is some evidence that, melatonin improves the decline in certain brain functions and immunity that occurs with aging , **(4)**. As well as melatonin has the ability to penetrate most tissues of the body and into the intracellular spaces. Such widespread distribution would be necessary to affect the rate of aging, assuming that aging is indeed caused by such processes *(5)*. Accordingly, the present study was carried out to investigate the effect of aging, as well as the effect of melatonin on the level of heart, lung and kidney antioxidants and lipid peroxidation of aged male rats.

MATERIAL AND METHODS

Thirty six male albino rats of different ages were selected and divided into three equal groups (12 rat/group) the first group (GI) acted as control young male rats (2-4 months old) not supplied by any additive. The second

Group (GII) acted as control aged male rats (18-27 months old) not supplied by any additives. The third Group (GIII): aged male rats (18-27 months old) supplemented with melatonin orally at a dose of 0.27 mg/Kg body weight daily for 120 days. The doses were calculated according to *(6)*. Soon after the animals were killed, the heart, lung and kidney were rapidly removed, washed with physiological saline weighted, and homogenized directly by electric homogenizer using an ice cooled 20 mM tris Hcl buffer pH 7.4 containing 0.15 m Kcl then centrifuged at 3000 xg. for 15 min at 4°C *(7)*. The supernatant obtained was used freshly to determine the activities of Cu /Zn SOD *(8)*, (GSH_{PX}) *(9)* and catalase *(10)*. Reduced glutathoine (GSH) was determined spectrophotomertically using glutathione reductase and 5.5' dithiobios (2-nitrobenzoic acid as described by *(11)*. Tissue lipid peroxidation as (MDA) was measured spectrophotometerically after the reaction with thiobarbituric acid. Total protein concentration were determined using method of *(12)*. Specimen were collected from the heart, lung and kidney, fixed in 10% neutral buffered formalin, dehydrated , cleared , embedded in paraffin and then sections of 5 um were prepared and stained with hematoxalin and eosin and examined microscopically according to *(13)*. Statistical analysis of the data was performed using student t-test *(14)*.

RESULTS

Table (1) showed that aging induce a highly significant decrease in the heart and lung Cu/Zn SOD and a significant decrease in that of the kidney compared with young control group. While melatonin produces a significant increase in heart and lung Cu/Zn SOD of aged rats compared with aged control group. Also there were a significant decrease in heart and lung and highly significant decrease in kidney (GSH_{PX}) activity of aged rat compared with young control group. While melatonin produces significant increase in the heart, lung and kidney (GSH_{PX}) activity of aged rats compared to aged control group. Heart catalase activity of aged rat showed a significant decrease compared with young control group. Melatonin induced a significant increase in heart catalase activity compared to aged control group.

Table (1): Effect of melatonin on tissues, Cu/Zn SOD, GSH_{PX} and catalase activities of aged male rats

Parameter Groups	Cu/ZnSOD (u/mg protein)			GSHpx (u/mg protein)			Catalase(u/mg protein)		
	Heart	lung	kidney	Heart	lung	kidney	Heart	lung	kidney
GI	32.11 ± 3.37	48.73 ± 4.17	11.89 ± 2.15	44.01 ± 3.11	22.69 ± 2.12	166.72 ± 11.01	35.73 ± 2.43	23.51 ± 2.19	4.22 ± 0.93
GII	13.89** ± 1.03	22.99** ± 2.13	5.79* ± 0.99	31.06* ± 1.82	12.95* ± 1.05	97.15** ± 7.87	23.19* ± 2.65	21.18 ± 1.77	3.00 ± 0.44
GIII	21.02 ± 2.02	33.19+ ± 1.79	6.97 ± 0.81	39.58+ ± 1.65	19.86+ ± 9.87	132.50+ ± 9.87	33.59+ ± 2.03	25.04 ± 2.43	3.55 ± 0.95

*Significant different from control young

+Significant different from control aged

** High Significant at ($P< 0.01$)

Table (2): Effect of melatonin on tissues GSH Concentration and lipid peroxidations of aged male rats .

Parameter / Groups	GSH *(µmol/* mg protein)			MDA (n mol/ mg protein)		
	Heart	Lung	Kidney	Heart	Lung	kidney
GI	11.65±1.01	10.79±1.09	13.76±1.12	0.25±0.05	0.96±0.06	0.68±0.014
GII	7.19*±0.63	7.67±0.85	8.12*±0.69	0.53*±0.08	1.89*± 0.091	0.83**±0.021
GIII	9.96^{+}±0.91	9.00±0.93	11.89^{+}±0.79	0.29^{+}±0.04	1.11^{+}±0.08	0.74^{+}± 0.013

*Significant different from control young + Significant different from control aged

Table (2) exhibits a significant decrease in heart, kidney GSH level of aged rats compared to young control group. Administration of melatonin produces a significant increase in heart and kidney GSH concentration when compared with aged control group. A highly significant increase in kidney and significant increase in heart and lung MDA level of aged rats compared with young group. While administration of melatonin produce significant decrease in heart, lung and kidney MDA of aged rats compared with aged control group.

Histological findings

Group (1), control young rats

The heart, showed branching myocardial muscle, distinct striation with homogenous eosinophilic cytoplasm and one to two basophilic centrally located nuclei (Fig.1). The lung of the rat showed circumscribed alveoli , alveolar duct and alveolar sacs. The alveoli were lined by simple squamous and low cuboidal epithelial cells with acidophilic cytoplasm and large centrally located nuclei. (Fig.2). The kidney renal tubules characterized by well developed renal corpuscle, proximal and distal convoluted tubules in the cortex (Fig.3).

Group (2), aged rats

The heart showed some histological changes which included loss of the striation in some myocardial bundles (Fig.4). Some muscles fibers appeared structurless with dark eosinophilic cytoplasm and necrotic nuclei. Intramuscular hemorrhage was appeared between the myocardial muscle .The lung showed thickening in the inter-alveolar septum with deposition of lymphocytes between the alveoli. Increase in size and fusion of some alveoli. Desquamation of some epithelial cells lining the bronchioles indicated in the lung tissue (Fig.5). Some alveoli were destructed and fragmentation of its contents was spread between the alveolar tissues. The renal corpuscle showed minute histological changes which include detachment of some squamous cells of the parietal layer of the Bowman's capsule. The obvious histological changes located in both proximal, distal convoluted tubules and the collecting duct. Sparsely degranulation noticed in the cytoplasm of the tubules with loss of the cell boundaries (Fig.6). The nuclei appeared dark basophilic with no histological changes.

Group (3), melatonin administrated aged rat

The heart showed histological changes, the affected myocardial muscle returned back to the normal histological structure although some myocardial muscle characterized by loss of striation and loss of the branching criteria of the myocardial muscle (Fig.7). The intramuscular hemorrhage was not evident. The lung returned back to the normal histological structure. While some histological changes still located as inter-alveolar hemorrhage and lymphocytic infiltration in the inter-alveolar septum (Fig.8). The renal tubules and ducts showed great histological improvement in the structure of the tubules, ducts and the corpuscle. But some renal tubules still destructed in spite of the great improvement (Fig.9).

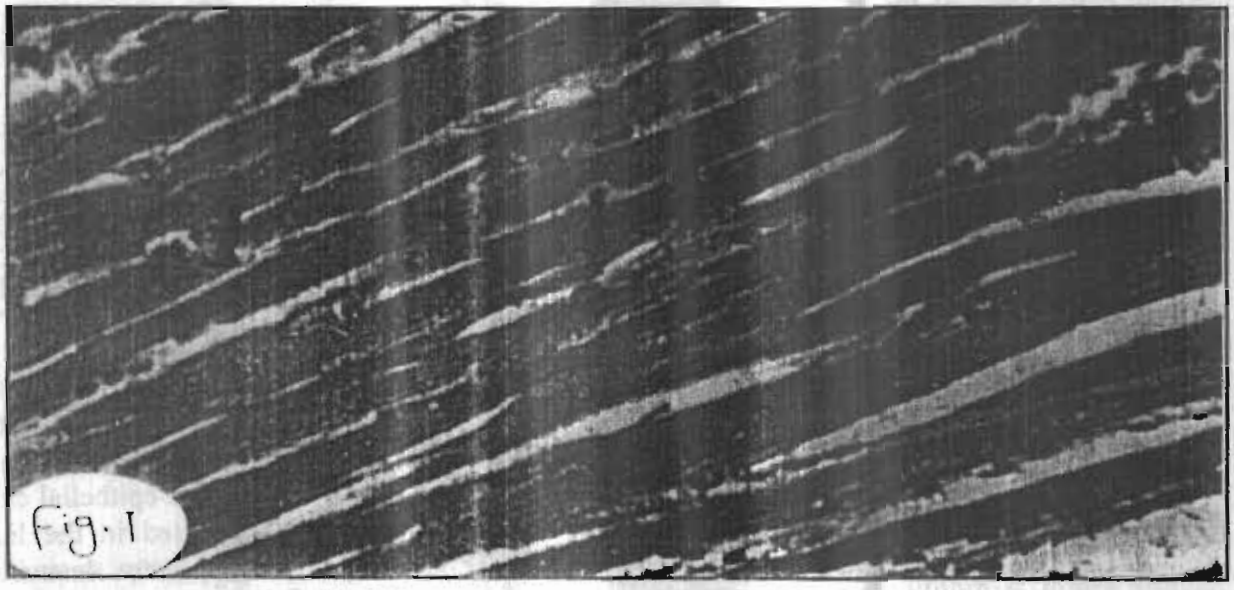

Fig.1: Photomicrograph of the rat heart of the (group.1) showing; the myocardial muscle fibers (M). striation (S) and branching (B). H&E .X400

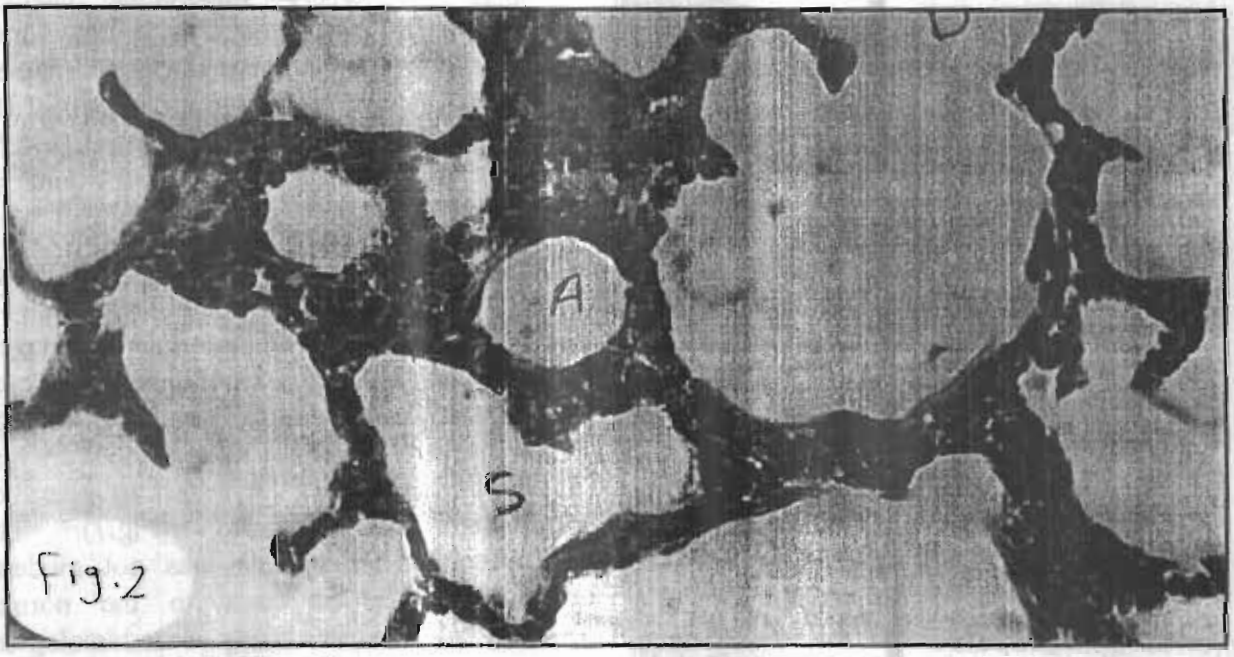

Fig. 2: Photomicrograph of the rat lung of the (group.1) showing; the alveoli (A), alveolar duct (D) and alveolar sac (S). H&E .X400

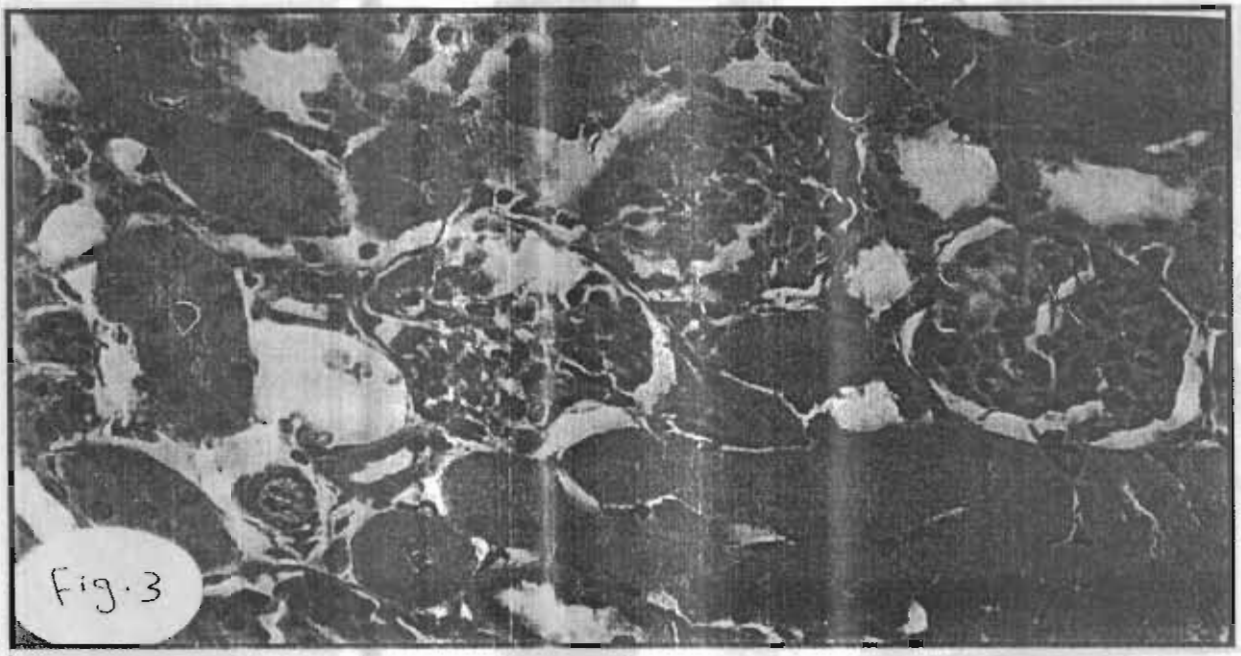

Fig.3: Photomicrograph of the rat kidney of the (group.1) showing; the renal corpuscle (R), proximal convoluted tubules PCT (P), distal convoluted tubules (D) and the collecting ducts (C). H&E .X400

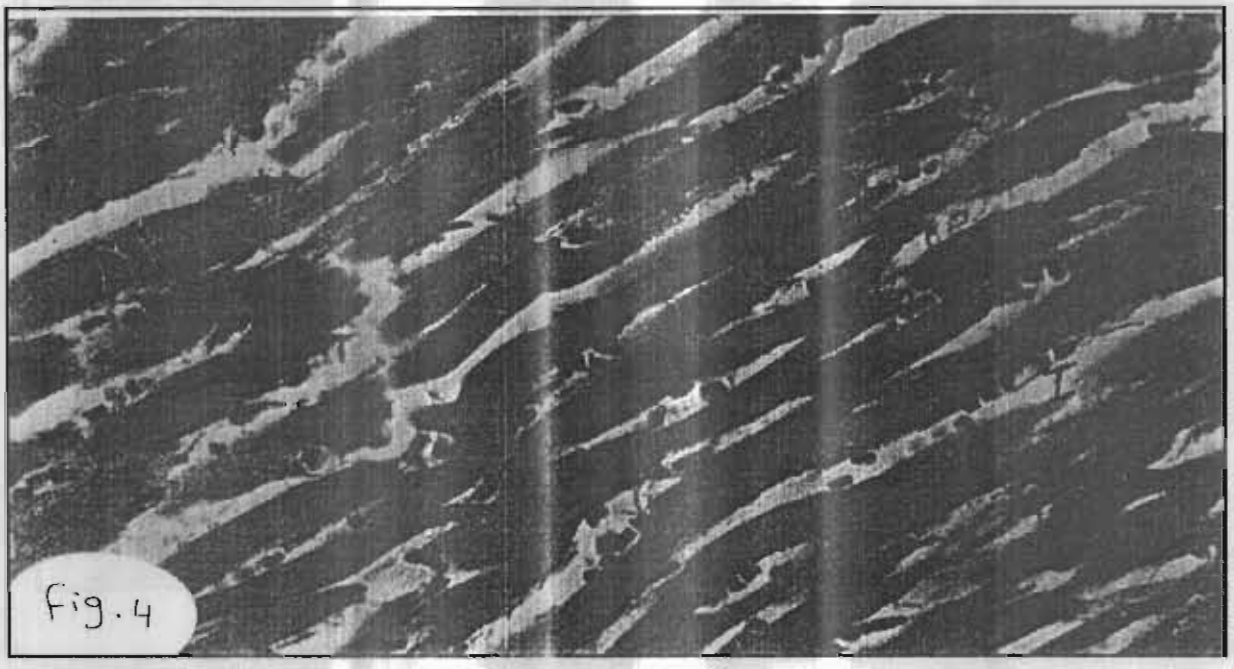

Fig.4: Photomicrograph of the rat heart of the (group.2) showing; the lost striation of the myocardial muscle fibers (M). H&E X400

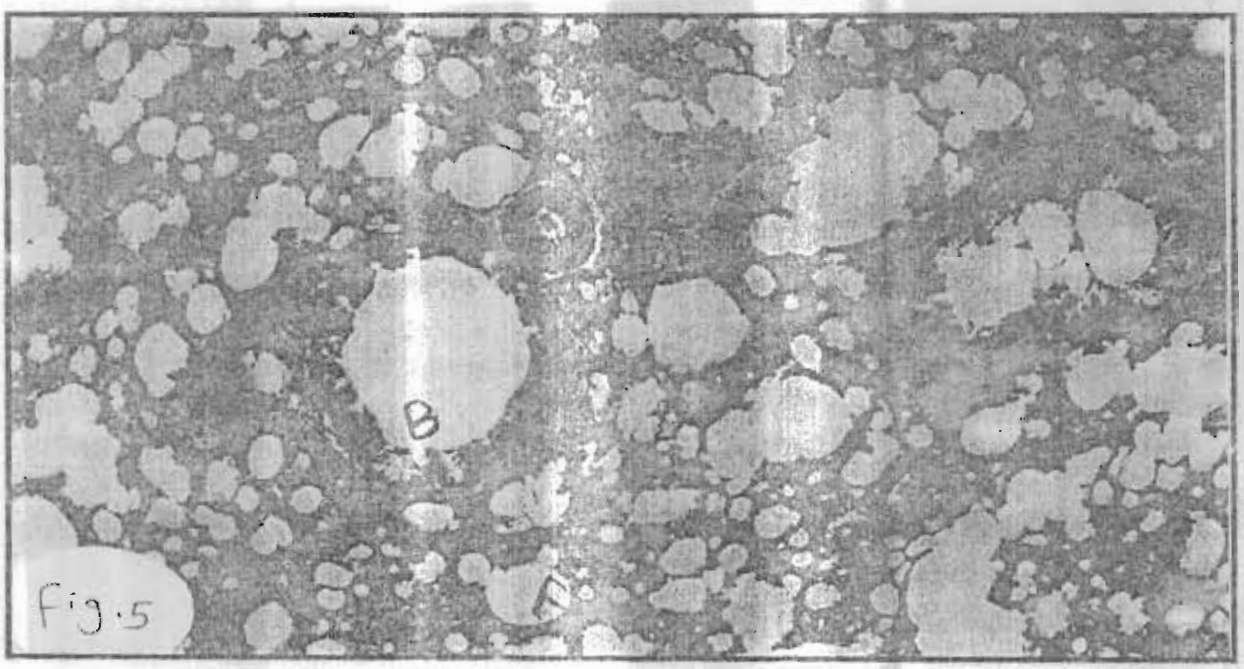

Fig.5: Photomicrograph of the rat lung of the (group.2) showing; the destructed alveoli (D). desquamated bronchial epithelium (B) and thick interalveolar septum (T) H&E .X100

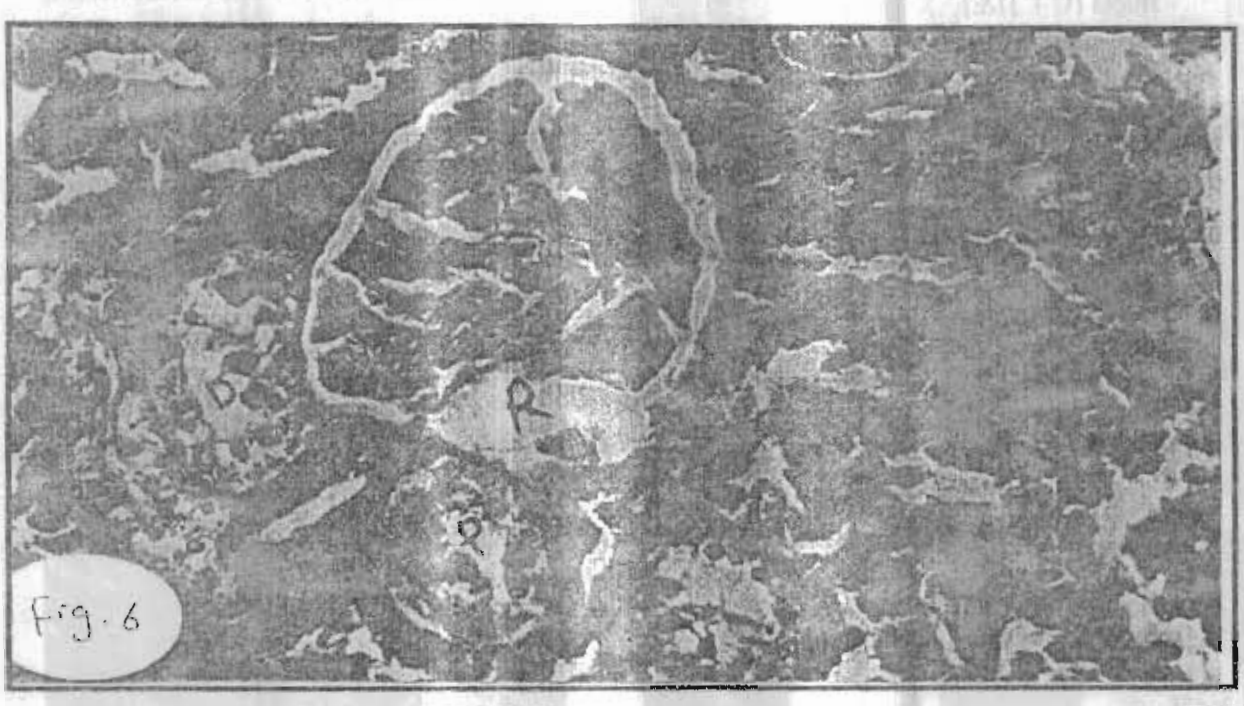

Fig.6: Photomicrograph of the rat kidney of the (group.2) showing; the epithelial loss of the renal corpuscle (R) and sparsely degranulated cytoplasm of the PCT (P), (D) and the collecting ducts (C). H&E X400

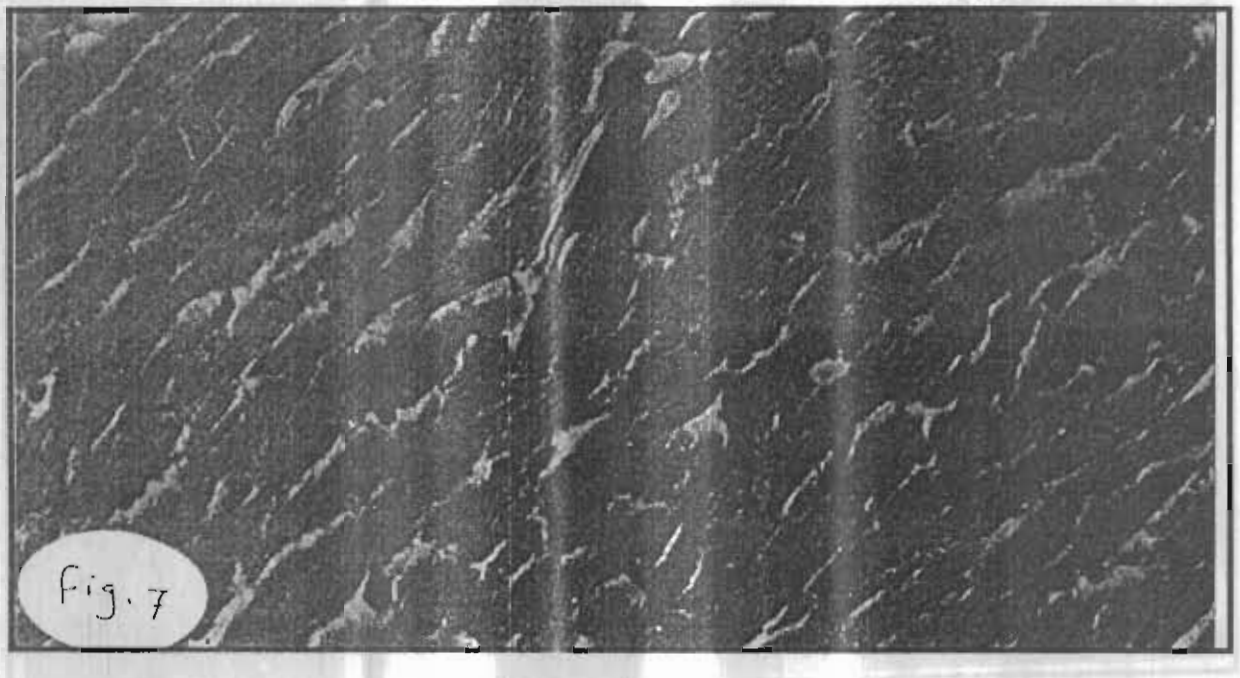

Fig.7: Photomicrograph of the rat heart of the (group.3) showing; the myocardial muscle (M), striation (S) and loss of muscle branching (B). Note, no intramuscular hemorrhage (Arrow) H&E X400

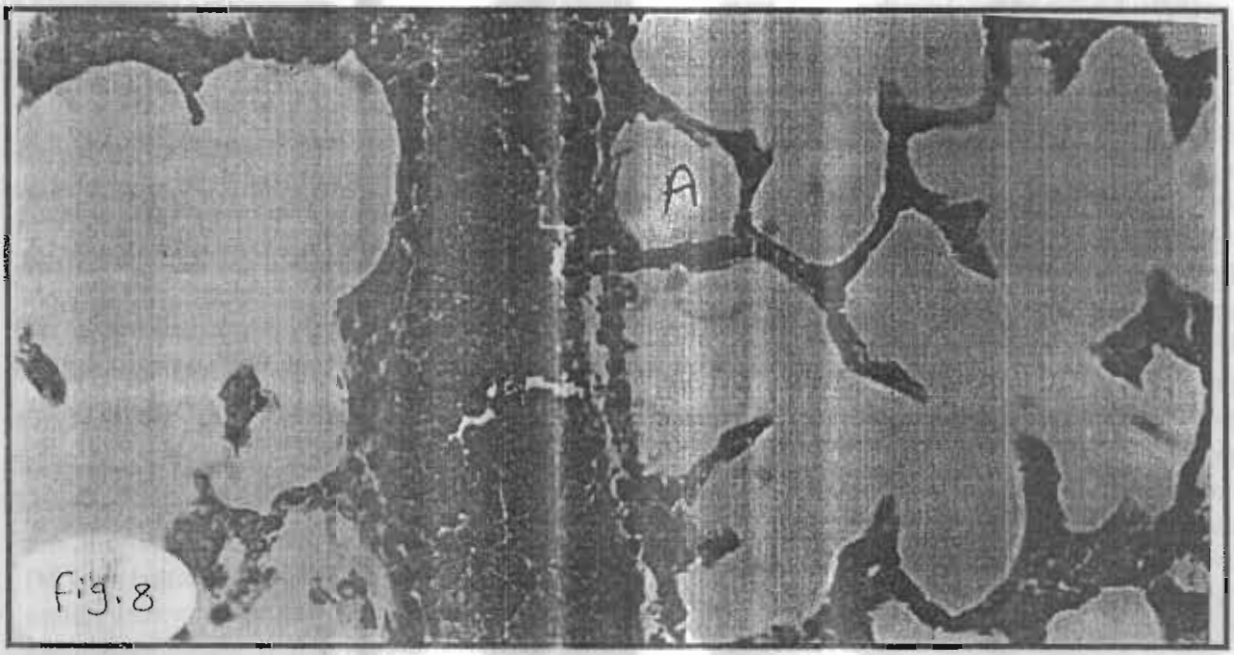

Fig.8: Photomicrograph of the rat lung of the (group.3) showing; the alveoli (A), congested blood vessels (H) H&E X400

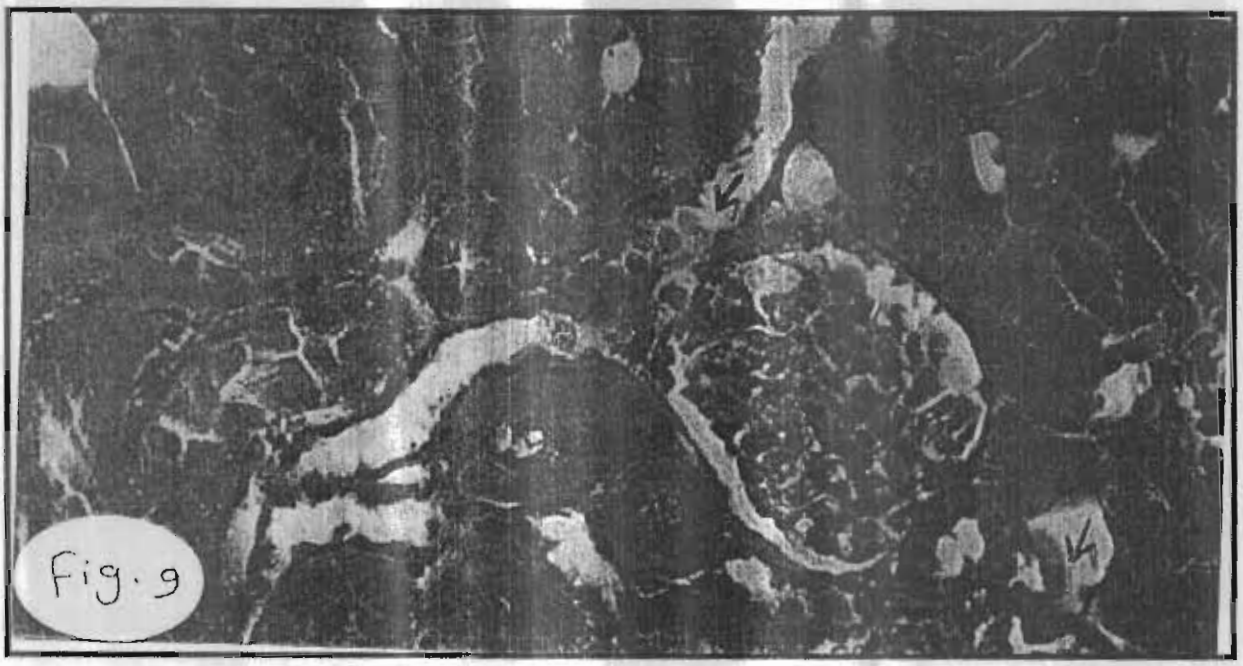

Fig.9: Photomicrograph of the rat kidney of the (group.3) showing; the improvement of the PCT (P) and DCT (D) and collecting ducts (C). H&E X400

DISCUSSION

The obtained results revealed significant decrease in the heart, lung and kidney Cu/Zn SOD and GSH px activities of aged male rats, these results were came in accordance to that of **(15)** who reported that, aging is usually accompanied with hypometabolic state, including alterations in antioxidant enzymes activities, such as SOD, CAT and GSHpx which had a vital role in protecting tissues from oxidative damage *(16)*. As their during aging depletion increase the vulnerability of cellular component to reactive oxygen species resulted in promoting the free radical damaging effect via increasing the level of oxidation *(17)*, and imbalance between the formation and removal of reactive oxygen species (ROS), that plays an important role in age-associated diseases *(18)*

It might be explained by taking the free radical theory of aging in consideration *(19)*, as those free radicals resulted in the formation of protein peroxide, as well as inactivation of detoxifying enzyme such as GSHpx via splitting of the peptide chain *(20)*

The significant decrease in heart catalase activity of aged male rats was similar to the data obtained by *(21&22)* who showed remarkable decrease in the left and right ventricle of the heart catalase activity of aged rats. These results could be attributed as the heart faces a high risk of free radicals injury, owing to slow generation of antioxidant enzymes by its cell. A general decline in this system may be a reason for the development of age related disease *(23)*

Concerning the effect of melatonin, our results were similar to those obtained by *(24)* who concluded that, melatonin is a very potent and efficient antioxidant, it confer protection against the oxidative damage through, its electron rich molecule, that may interact with free radicals forms many metabolites, which are also effective free radicals scavengers.

This continuous process of trapping of unpaired electron free radicals by melatonin and its metabolites have been defined as a scavenging cascade reaction, *(25)* . Alternatively, melatonin may stimulate several antioxidative enzymes and inhibit the prooxidative enzyme, nitric oxide synthase *(24)*. Induction of antioxidant enzymes such as SOD, catalase and GSH_{PX} via specific melatonin receptors and stimulation of gene expression for antioxidant enzymes through increase the level of m RNA for GSH_{PX} and SOD in tissue *(26)*

Besides the ability of melatonin to detoxify a variety of reactive, oxygen free radicals, it also indirectly reduces molecular damage via stimulating the metabolism of potentially toxic molecules to non-toxic products *(27)*.

With respect to the significant decline in heart and kidney GSH concentration of aging male rats. It could be attributed to over production of free radicals, leading to depletion of cellular stores of antioxidant *(28)*, such as reduction of glutathione reductase (GR) activity or extensive utilization of GSH in scavenging free radicals. *(29)* by allowing the hydrogen of SH group to be abstracted instead of unsaturated fatty acids *(7)*.

Regarding the effect of melatonin administration, our data were came in accordance to those reported by *(30)* who showed that, melatonin significantly increased the cardiac GSH content by 39% in swiss albino mice, as it is effective in protecting nuclear DNA and induction of antioxidant enzymes such as catalase, SOD, and (GSHpx) via specific melatonin receptors *(24)*. Moreover, it increase the activity of GR which is necessary for conversion of GSSG to GSH, as GR posses a critical sulphydryl group at its active site, participate in the reduction of oxidized glutathione *(31)*. Melatonin, also stimulate gamma-glutamyl cysteine synthase, the rate limiting enzyme in the production of an important antioxidant, reduced glutathione (GSH) *(30)*.

The recorded significant increase in tissue MDA of aged male rats were nearly similar to the results reported by *(32&33)* who showed a significant increase in lipid peroxidation evidenced by higher MDA in the heart of 22 month old rats. Furthermore *(29)* recorded a significant increase in the level of tissue MDA of aged rats compared with young group. They attributed these results to increased ROS generation, to an extent that overcome the cellular antioxidants, resulted in oxidative stress *(34)*. Moreover ROS alter proteins, carbohydrates, and lipids, and inactivates enzymes and transporters, damages DNA and initiates the chain reactions that peroxidize polyunsaturated fatty acids in membrane phospholipids *(35)*. As well as production of aldhydic compounds *(36)*, such as MDA which considered one of the bio-product in lipid peroxidation and a marker of oxidative stress *(37)*

Concerning melatonin effect in lipid peroxidation, our results were supported by *(38)* who demonstrated that, pretreatment with melatonin protected against the development of acute tubular necrosis and improved renal function and lipid peroxidation caused by oxidative stress due to renal ischemia .

Melatonin has been found to protect the cell from oxidative stress induced by a variety of free radical generating agents via preserving the functional integrity of membrane lipids. *(39)* and inhibition of nitric oxide synthase enzyme (NOS), that generate nitric oxide which can degraded into highly toxic hydroxyl radical in the presence of superoxide anion. *(24)*..

Histologically melatonin had an effective role against the damage occur to the renal tissue due to advanced age or other harmful factors *(40& 41)* and in the lung tissue due to effect of cadmium administration *(42)* and in the heart under effect of some toxins *(43)*

Melatonin's role in reducing lipid peroxidation was assured by the fact that, it scavenges O2, and OH, which are sufficiently

reactive to initiate the peroxidative process. Moreover melatonin functions as a chain breaking antioxidant by directly scavenging the LOO *(44)*. As it is twice as effective in scavenging the LOO. as vitamin E, the primer chain-breaking antioxidant. This finding, would make melatonin the most effective chain breaking antioxidant discovered to date.

CONCLUSION

It could be concluded that, melatonin reduce, the heart, lung, and kidney damage caused by oxidative stress induced by aging through 120 days. Thus it may be represent a novel therapeutic approach for prevention of tissue injury caused by aging. Consequently melatonin could be successfully used in prophylaxis and treatment of various diseases of elderly persons.

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الملخص العربى

تأثير تناول الميلاتونين على ضغوط الأكسدة الناتجة عن التقدم فى العمر فى ذكور الفئران

عفاف دسوقى عبد المجيد - حسام فؤاد عطية

قسم الكيمياء الحيوية وقسم الانسجه والخلايا- كلية الطب البيطرى بمشتهر

جامعــة بنهــا

يعتــبر تقدم العمر من المشاكل الكبيرة فى هذه الايام وذلك نتيجة للاجهاد البدنى والنفسي بجانب الــتلوث البيئى لذا تم دراسة تأثير تناول الميلاتونين على ضغوط الاكسدة الناتجة من التقدم فى العمر. تم أخــذ عيــنات من القلب والرئة والكلى بعد انتهاء فترة التجربة وذلك لقياس نشاط أنزيمات السوبر أكسيد ديسميوتيز والجلوتاثين بيروكسيديز والكتاليز بالإضافة إلى تركيز الجلوتاثيون المختزل وأيضا فوق اكسيد الدهــون فى تلك الانسجة. وقد أظهرت النتائج أن تقدم العمر يكون مصحوبا بنقص فى نشاط الإنزيمات المضــادة للأكســدة مــثل إنزيم السوبر اكسيد ديسميوتيز والجلوتاثين بيروكسيديز والكتاليز وأيضا نسبة الجلوتاثيون المختزل فى الأنسجة ويظهر في الانسجه علي شكل تغير في العضلات القلبيه كما يؤدي الي تكسير في الحويصلات الهوائيه والأنابيب الكلويه.

كمــا أظهرت أن تناول الميلاتونين يؤدى إلى تعديل هذه التغيرات كما يقلل من نسبة المالوداى الدهــيد والــذى أدى الــتقدم فــى العمر إلى زيادته بالأنسجة علاوة على ذلك فانه يحسن من التغيرات الهيستولوجية. مما تقدم يتضح لنا أن هناك دورا حيويا للميلاتونين فى حماية الأنسجة من التلف الناتج عن ضــغوط الأكسدة عند التقدم فى العمر حيث انه يعدل التأثيرات الغير مرغوب فيها الناتجة عن التقدم فى العمر وبذلك يتغلب على أعراض الشيخوخة.