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PROTECTIVE ROLE OF MELATONIN ON SOME BIOCHEMICAL ASPECTS OF NICOTINE ADMINISTRATION ON BRAIN OVARIECTOMIZED FEMALE RATS

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Abstract

The protective effect of melatonin against the damage of nicotine on the brain in ovariectomized female rats (OVX) was investigated. Cigarette smoking is common in societies worldwide and has been identified as injurious to human health. The data revealed that nicotine,a major component of cigarette smoke (at a dose of 2 mg/ KG b.wt.) resulted in a significant increase in total proteins, lipid peroxides (LPO), total cholesterol and phospholipids, and a significant decrease in acetylcholenesterase activity (AChE) and glutathione content (GSH).

Melatonin administration at dose (5 mg/kg b.wt.)to nicotine treated rats showed significantly ameliorated changes in total proteins, acetylcholenesterase (AChE) , glutathione content (GSH) , lipid peroxides (LPO) , total cholesterol (TC) and phospholipids (Ph). The obtained results suggest that the protective effect of melatonin is mediated through decreased oxidation of lipids , thus minimizing the risk posed by nicotine .

Introduction

Nicotine, is one of the major hazardous components present in cigarette smoke and tobacco , plays an important role in the development of cardiovascular disease and lung cancer in smokers (Ashakumary and vijayammal, 1997; Howard *et al*.,1998;Carpagnano, *et al*., 2003 and Hackett *et al*.,2003).

However, cigarette smoke has been established as a major risk factor for atherosclerosis and lung cancer (Latha *et al*.,1992). Nicotine could play a role in atherosclerosis and contribute to acute cardiovascular events via its hemodynamic effects (Benowitz, 1997; Chan & Dimich, 2003).

In addition to its hemodynamic effects, tobacco not only has an atherogenic effect (endothelial toxicity and changes in lipid profile), but it also facilitates thrombosis and spasm (Thomas, 1993). Latha *et al*. (1993) and Ashakumary & Vijayammal, (1997) reported that nicotine administration to rats is associated with significant alterations in serum & tissue levels of lipids and lipoproteins, suggesting that nicotine may therefore , contribute at least partly to the risk posed by cigarette smoking in the development of atherosclerosis. However, the mechanisms responsible for the changes in lipids and lipoproteins are poorly understood (Criag , 1993) .

In addition , lipid peroxidation is a process associated with the pathogenesis of atherosclerosis . Nicotine administration as well as cigarette smoking increased the level of lipid peroxides and the production of reactive oxygen species that may contribute to the development and/or progression of cardiovascular disease (Ashakumary and Vijayammal, 1996; Al–Senaidy *et al*., 1997; Helen *et al*., 1999 and Gary & Christina, 2007).

Klevens *et al*., (1995) discovered that cigarette smoking causes a dramatic decrease in the levels of an important enzyme that breaks down dopamine. Parkin *et al*. (1994) reported that nicotine increased Cholinergic activity which causes apoptosis (programmed cell death).

Since apoptosis helps to remove mutated or damaged cells that may eventually become cancerous, the inhibitory actions of nicotine create a more favourable environment for cancer to develop. Thus nicotine plays an indirect role in carcinogenesis . It is also important to role that its addictive properties are often the primary motivating factor for tobacco smoking, contributing to the proliferation of cancer (Parkin *et al*. 1994).

However, Zhu *et al*. (1996) noted that the majority of people diagnosed with schizophrenia smoke tobacco and for the number of schizophrenics that smoke range from 75% to 90%. it was recently argued that the increased level of smoking in schizophrenia may be due to a desire to self – medicate with nicotine.

However, Moran *et al*.(2003) reported that women smokers are more aware of their increased risk for developing lung cancer than their increased risk for developing heart disease or osteoporosis.

Waterlow *et al.*, (1978), Goldspink & and Kelly,(1984). Attaix *et al*. (1988) and Sunok *et al*., (2002) found that the rate of protein synthesis in the brain decreased with age in rats after ovariectomy. Also, Sowers (1996) investigated that not only age but also sex hormone deficiency has been shown to affect body composition and functional in postmenopausal women. Estrogen increases tissue protein synthesis by stimulating transcriptional activity (Villa *et al*., 1995 and Hofbauer *et al.,* 1999). Also, Hayase *et al*. (2001) reported that estrogen increased protein synthesis in the brain of ovariectomized female rats.

Many chemicals, drugs or smoking and radiation are known as mutagens or carcinogens.Intrinsic cellular mechanisms are engaged in cell repair, either enzymatically or via cellular reductants including glutathione and catalase which

combat oxidative damage of either interacellular metabolism or induced by extrinsic factors. Reactive free radicals are produced continuously in the body as a result of normal metabolic processes (Kehrer, 1993). extensive amounts of reactive free radicals have harmful effects that ultimately, if not removed, lead to cell damage ,mutation and cancer (Krinsky,1989) .

Melatonin, a natural endogenous product of the pineal gland, is a highly effective antioxidant. Also, melatonin has been reported to alter the activities of enzymes which improve the total antioxidative defense capacity of the organism, i.e. glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase . (Reiter *et al*., 1997).

Hsu *et al.* (2000) studied the protective effect of melatonin, vitamin C and beta carotene against Phosphine (an insecticide and rodenticide) – induced oxidative damage in brain, lung and liver of rats. Hsu *et al.*(2000) found that melatonin significantly or completey bloked the induced oxidative damage by phosphine while, vitamin C and beta-carotene were less effective or inactive.

Agapito *et al.* (2001) observed that oxidative damage iduced by the antitumor drug, adriamycin, could be reduced by low pharmacological doses of melatonin. Moreover, vascular endothelial growth factor is the most active angiogenic factor, and the evidence of abnormally high blood levels, has been proven associated with poor prognosis in cancer patients. Melatonin was observed to control tumor growth at least in part by acting as a natural anti- angiogenic molecule (Lissoni *et al*., 2001).

Melatonin reduced cadmium- induced lipid peroxidation in hamster brain, heart, kidney, lung and liver(Karbownik *et al*.,2001) and also prevented DNA damage induced by the pesticide, or ultraviolet radiation. Yamamoto and Mohanan, (2001) and Sener *et al.* (2002) reported that melatonin improves oxidative damage in the liver, lung and intestine induced by burn injury in rats.Furthermore, Karaoz *et al.* (2002) revealed that high doses of Vitamin C plus Vitamin E and melatonin considerably reduced chlorpyriphos-ethyle toxicity in lung tissues of rats. Exogenously administered melatonin effectively protected lungs from reperfusion injury after prolonged ischemia (Inci *et al*., 2002). Lissoni *et al*., (2003) suggested a new biochemotherapeutic strategy in the treatment of human neoplasms. Karaoz *et al.* (2002) found that chemotherapy was better tolerated in metastatic non-small cell lung cancer patients treated with melatonin. They also reported that melatonin modulated the effects of cancer chemotherapy, by enhancing its therapeutic efficacy and reducing its toxicity.

Accordingly, melatonin might be effective in ameliorating the progression of brain injury associated with nicotine administration. Thus, the present study was performed to investigate the possible protective effect of melatonin against nicotine-induced brain tissue injury.

Material And Methods

Adult sixty female rats weighting about 120 – 140 g were used in the present study, standard diet was provided and water was available *ad libitum*. After one week of acclimatization to the laboratory environment, ten animals were served as control while other animals were ovariectomized according to the method of Agmo, (1997). Female rats were anesthetized with light diethyl ether anesthesia. With the female in a prone position, a medial dorsal incision, about 1.5 cm, long was made midway between the last rib and the knee. The skin was then pulled about 1 cm to the left and a second incision was made through the muscle layer into the peritoneal cavity. The ovaries were located through visualization of the peri-ovarian fat, prior to removal. The fat was withdrawn, The ovary was separated and the oviduct legated with silk 4.0. The ovary was cut away and the incision sutured. The ovary on the opposite side was then removed similarly through a separate incision wound closure included cut gut 4.0 for (internal) and 2.0 for (external). After two weeks from ovariectomized rats were classified into:

Group: 1: Control rat and administered distilled water
Group: 2: Ovariectomized female rats (OVX).
Group: 3: Ovariectomized+ nicotine (OVX+N).
Group: 4: Ovariectomized+ melatonine (OVX+M).
Group: 5: Ovariectomized+ nicotine + melatonine (OVX+N+M).

Nicotine was obtained from Hopkin Williams and LTD, England and was daily intrapertioneally injected at a dose of 2 mg/kg body weight for 4 weeks. Melatonin was obtained from Amoun ltd.co. Egypt in very fine powder dissolved in distilled water and given in dose of 5 mg /kg body weight for 4 weeks.

At the end of this experiment, the rats were sacrificed, the brains were isolated, weighted and homogenized for biochemical determinations according to Glowinski and Iversen (1966).Total protein content was determined by Lowry *et al*.(1951), the activity of acetylcholinesterase (AChE) in the brain was determined by the method of Gorun *et al*. (1978).

The glutathione (GSH) content in tissue homogenates was estimated by the method of Beutler (1982), the lipid peroxides (LPO) by the method of Uchiyama and Mihera (1978),total cholesterol (TC) was measured according to Allain et al. (1974), triglycerides by using the method of Wahlefeld, (1974) and phospholipids by the method of Raheja *et al*. (1973).

Statistical analysis:-

Data were expressed as means ± standard error(SE) student t- test was used to elucidate the differences between treated and control group (Murray,1982). Adifference was considered significant at $P< 0.05$.

Results

Table (1) represents the brain weight and total protein content, Acetylcholenesterase activity (AChE) and glutathion content in brain tissue. The data reveals that, the ovariectomized female rats and ovariectomized treated with melatonin showed non – significant changes in the measured parameters compared to control rats.

Nicotine intrapertioneally showed a significant a increase in total proteins content, and a significant decrease in acetylcholenesterase activity (AChE) and a glutathione content (GSH) while the brain weight showed no change when compared to control. Supplementation of melatonin to ovariectomized nicotine treated rats showed a mild increase but significant decrease compared to control rats in all the measured parameters.

Table (2) represents the changes in the lipid peroxidase, triglyceride, total cholesterol and phospholipids in brain tissue of different animal groups.

Resultes in table (2) reveals that, the group of ovariectomized female rats treated with nicotine showed a significant increase in lipid peroxidase triglycerides, total cholesterol and phospholipids when compared with control group. However, ovariectomized female rats treated with nicotine and supplementation melatonin showed mild significant increase in all the measured parameters compared to control rats.

On the otherhand, the present data reveal that, the ovariectomized and the ovariectomized supplementation melatonin female rats showed non significant changes in all the measured parameter compared to control group.

Table (1): Effect of different treatments on the (brain weight, total protein content-acetylcholenesterase activity and glutathione content) in the brain female ovariectomy rats.

Criteria / parameters	Control	OVX	OVX+N	OVX+M	OVX+N+M
Brain weight (g / tissue)	0.73±0.0 3	0.72±o.o4	0.75±0.03	0.74±0.02	0.77±0.02
Total protein (mg/g tissue)	28.00±0.18	27.69±0.43	38.24±0.56*	27.48±0.43	25.36±0.31*
Acetylcholenesterase (µ mole/gm tissue)	11.92±0.11	11.53±0.10	9.63±0.30*	11.46±0.17	8.49±0.40*
GSH content (mg/g tissue)	0.53±0.02	0.52±0.02	0.16±0.02*	0.55±0.02	0.29±0.01*

- All values represent the mean ± S.E of 6 animals

*Significant at P <0.05

OVX= Ovariectomized female rats.

OVX+ N= Ovariectomized female rats + Nicotine.

OVX+M= Ovariectomized female rats + Melatonin.

OVX+N+M= Ovariectomized female rats+Nicotine+Melatonin.

Table (2): Effect of different treatments on the (lipid peroxidase level, triglyceride, total cholesterol and phospholipids) in brain female ovariectomy rats.

Criteria / parameters	Control	OVX	OVX + N	OVX + M	OVX+N+M
Lipid peroxidation nmol TBA /g tissue	187.56±0.87	187.96±0.47	219.27±0.34*	187.74±1.09	204.60±1.56*
Triglyceride (mg / g tissue)	2.18±0.10	2.78±0.04	3.28±0.04*	2.39±0.04	3.01±0.06*
Total cholesterol (mg / g tissue)	41.64±0.17	41.39±0.36	47.18±0.97*	41.19±0.66	44.66±0.58*
Phospholipid (mg / g tissue)	85.53±0.39	85.53±0.25	93.75±0.29*	85.67±0.37	89.96±0.31*

- All values represent the mean ± S.E of 6 animals

* Significant at P < 0. 05.

OVX= Ovariectomized female rats.

OVX+N= Ovariectomized female rats+Nicotine.

OVX+M= Ovariectomized female rats+Melatonin.

OVX+N+M=Ovariectomized female rats+ Nicotine+ Melatonin.

Discussion

The brain weight and some biochemical assay of brain ovariectomized female treated with nicotine and supplementent melation were investigated in the present study and compared to the control group.

Melatonin is a very potent and efficient endogenous free radical scavenger. It reacts with the highly toxic hydroxy radical and provides on site protection against oxidative damage to biomolecules within every cellular Compartment. Melatonin acts as a primary non–enzymatic anti oxidative defense against the devastating actions of the extremely reactive free radicals (Burkhard *et al*., 1993; Kazez *et al.,* 2000 and Hara *et al.,* 2001). Melatonin biosynthesis has been found to be decreased in old rats (Hardeland *et al*., 1993 and Delbarre *et al.*, 1992).

In the present study, the ovariectomized female rats with nicotine caused a significant increase in total proteins content. While supplementation of melatonin caused a significant decrease which recorded and this finding is in agreement with Touitou *et al*.,(1996) and Brzezinski, (1997). They reported discrepancy effects of exogenous melatonin and its beneficial role in biological regulation of circadian rhythms, sleep, mood, and perhaps reproduction, tumour growth and ageing.

On the otherhand, the present data showed a decrease in GSH content and this finding agreement with Change *et al*., (1998). Gamal *et al*. (2007) reported that the reduction of tissue glutathione has been interpreted as an indicator of significant oxidant stress. Therefore, AChE activity recorded a significant decrease in the brain tissue in comparison with control rats. Finberg *et al* .(1979) reported that some drugs such as nicotine which activate post – synaptic dompamine such as L–dopa and apomorphine inhibit the release of ACh(neurotransmitter) from brain .

In the present study the data revealed that elevation of lipid peroxidise (LPO) , triglyceride, total cholesterol and phospholipids in the brain tissues of ovariectomized female rats treated with nicotine. These results are in accordance with the observations of Allen *et al*.(1994) who reported a significant increase in total cholesterol , phospholipids and triglycerides in most of the tissues of rat and sera of nicotine treated rats. However, the changes produced in lipids fractions in nicotine administration were similar to those observed on exposure of rats to cigarette smoke (Whittaker *et al*., 1996 and Gary& Christina, 2007), and it was felt that nicotine may therefore contribute at least partly to the risk posed by cigarette smoking in the development of atherosclerosis.

The hyperlipidemic effect of nicotine may be attributed to that nicotine increase the activity of insulin resistance leading to lipid disorders (Goldman &Klinger,1998).Nicotine administration was suggested to increase the synthesis of fatty acids in liver from carbohydrate and the mobilization of fatty acids from the depots to the liver (Lantner,1975). Tissues can synthesize fatty acids from acetyl CoA derived mainly from carbohydrates.

The main cause of impairment of acetyl CoA is intracellular carbohydrate deficiency probably induced by nicotine. Also, nicotine activates the sympathetic nervous system (by modification of action on catecholamine), where it elevated FFA, epinephrine and cortisol in the Blood of smoker (Criag, 1993).

The data of the present study are in agreement with the findings of Abd-el-Wahab (1997) who found that melatonin caused a marked decrease in parameters of hepatic damage and liver triglycerides but did not return to normal value. This protective effect of melatonin could be due to its ability to scavenge the free radical. Several authors reported that cholesterol and low density lipoprotein cholesterol (LDL-C) were reduced significantly by melatonin administration which participates in the regulation of cholesterol metabolism and in the prevention of oxidative damage to membranes Hoyos *et al*., 2000 and Sara *et al*., (2007). However, the melatonin administration was effective as antioxidant, although the protective effect of melatonin prevented the GSH decrease and reduced significantly the increases in enzyme activities and lipid peroxidation produced by biliary ligature (Lopez *et al*., 2000 and Gamal *et a*., 2007).

It could be concluded that melatonin is hypolipidemic effect of nicotine in ovariectomized female rats and may be useful in combating free radical-induced oxidative sress and tissue injury that is result of nicotine toxicity.

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الملخص العربي

الدور الوقائي للميلاتونين علي بعض التغيرات الكيميائية في مخ إناث الفئران المنزوعة المبايض والمحقونة بالبنيكوتين

أميرة تهامي إبراهيم مرسال

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يهدف هذا البحث الي دراسة الدور الوقائي للميلاتونين علي بعض التغيرات الكيميائية الناتجة من حقن مادة النيكوتين علي مخ إناث الفئران والمنزوعة المبايض .

وقد قسمت المجاميع الي خمس مجاميع وهي :

المجموعة الأولي : وهي المجموعة الضابطة وغير منزوعة المبايض

المجموعة الثانية : وهي المجموعة المنزوعة المبايض

المجموعة الثالثة : وهي مجموعة منزوعة المبايض وتم حقنها بمادة النيكوتين بجرعة 2 ميليجرام/كيلوجرام من وزن الجسم لمدة أربعة أسابيع .

المجموعة الرابعة : وهي مجموعة منزوعة المبايض وتم إعطائها مادة النيكوتين بجرعة 5 ميليجرام/كيلوجرام من وزن الجسم لمدة أربعة أسابيع .

المجموعة الخامسة : وهي مجموعة منزوعة المبايض وتم حقنها بمادة النيكوتين والميلاتونين .

وقد خلصت الدراسة الي النتائج التالية :

1 – أحدثت معاملة الفئران بالنيكوتين 2 مجم/كجم ارتفاعا ملحوظا في محتوي البروتين الكلي ومستوي الأكسدة الفوقية للدهون والكوليستيرول الكلي والفوسفوليبيدات بينما نقص نشاط انزيم الأستيل كولينيستيريز ومحتوي الجلوتاثيون .

2 – عند معامل الفئران بالميلاتونين 5 مجم/كجم لوحظ تسحن ملحوظ في مستوي المعايير السابقة.

وقد خلصت الدراسة الي أن استخدام مضادات الأكسدة ومن أهمها الميلاتونين له دور وقائي في الحماية من التعرض لأي ملوثات أو التدخين مع التقدم في العمر .