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Some Biochemical Studies On Blood And Brain Tissues Of Rats At Different Ages

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ABSTRACT

Eighty white male albino rats were used in the present study. These animals were classified according to their ages into 4 groups (2, 6, 12 and 24 months old rats) . Brain dopamine and serotonin content were decreased significantly at 24 months old rats . A significant increase in brain morepinephrine was recorded at 12 and 24 months old rats. Also the obtained data showed an increase of serum total cholesterol, HDL - cholesterol, LDL cholesterol, triacylglycerols , blood urea nitrogen, serum creatinine and uric acid at 6 , 12 and 24 months old rats . On the other hand , serum iron concentration , total iron binding capacity and the activity of glucose -6- phosphate dehydrogenase in the erythrocytes showed either insignificant or significant increases at 6,12 and 24 months old rats.

INTRODUCTION

Aging is generally considered to be characterized by a decreased ability to adapt to various forms of stimuli and a reduction in the ability of the aging organism to maintain the homeostatic equilibrium necessary to sustain life . The age - related decrease in homeostatic is related to a progressive increase in physiologic decrements that contribute to the senesence of the aging organism *(1)* .

Several theories have been proposed to explain the mechanism of aging. According to somatic mutation theory , random mutations accumulate in post - mitotic cells resulting into production of wrong proteins and a decrease in cell function. The error theory proposes that errors occur in amino acid sequences of enzymes like RNA polymerase and amino acyl RNA synthetase which are responsible for protein synthesis , such abnormalities may amplify the production of wornig proteins which on reaching critical levels make the cells function loss *(2)* .

Age - related alteration in function that place in the elderly at increased risk of serious clinical problems usually produce biochemical changes detectable by the laboratorian *(3)* .

Any study of the changes that occur with aging may offer insight into the central nervous system and may provide clues about the possible deterioration of synaptic function in which neurotransmitter mechanism play key roles *(4)*.

In our study we investigated biochemical parameters of rats blood (total cholesterol , high density lipoprotein cholesterol, triacylglycerols, serum iron , total iron binding capacity, blood urea nitrogen, creatinine, uric acid and glucose -6- phosphate dehydrogenase). In addition , dopamine , norepinephrine and serotonin content of whole brain tissue were also performed .

MATERIALS AND METHODS

Eighty white male albino rats were used in the experimental investigation of this study . The animals were kept at a constant ration and water was supplied adlibitum.

The rats were divided according to their ages into four main groups *(5)* , each consists of 20 rats and placed in individual cages :

Group I : Rats of two months old, representing young age and considered as control.

Group II : Rats of six months old and considered as adult age .

Group III : Rats of 12 months old and denoted as old age .

Group IV : Rats of 24 months old and representing the very old age.

The rats from each group were subdivided into two equal subgroups. The first subgroup was subjected to blood analysis . The sample collected contained 1 mg disodium ethylene diamine tetra acetic acid (EDTA) as anticoagulant for each 1 ml blood and processed directly for determination of glucose -6- phosphate dehydrogenase activity in erythrocytes *(6)* .

The second sample was taken without anticoagulant for serum analysis , total cholesterol, *(7)* , high density lipoprotein cholesterol *(8)*. Low density lipoprotein - cholesterol *(9)*. Triacyl-glycerols *(10)* iron, *(11, 12)*. total iron binding capacity (TIBC) *(13,14)*, unsaturated iron binding capacity (UIBC) *(15)* whose the saturation percent was claculated *(16)*.

Blood urea nitrogen *(17)* , creatinine *(18)*, uric acid *(19)* were also determined .

Brain tissue sample was obtained from each rat after it had been killed and processed directly for determination of dopamine, norepinephrine and serotonin *(20)* Statistical calculation were done *(21, 22 , 23)* .

RESULTS AND DISCUSSION

Table (1 & 2) showed a nonsignificant decrease of brain dopamine content at 6 months old rats, followed by very highly significant decrease at 12 and 24 months old. Several studies reported a significant decrease of dopamine content in different brain regions of rats *(5, 24)* . Accordingly , the present data could be attributed to the loss of dopanergic neurons with advancing age due to neuronal death as reported by *(25,26)* . This is consistent with *(27)* who found a reduction in the hypothalamus dopamine content of aged rats with no change in the activity of dopamine system and ascribed their results to a selective loss of neurons in several brain regions of old animals .

Our results may also be attributed to a decrease of dopamine autoreceptors which modulate the synthesis and release of dopamine as hypothesized by *(28)*.

The obtained data in tables (1 &2) showed a nonsignificant increase of brain norepinephrine at 6 months old rats, followed by a significant increase at 12 months, whereas this increase became very highly significant at 24 months old rats. Our results could be ascribed to the increase of uptake and storage processes of norepinephrine in certain brain regions. This hypothesis is confirmed by *(29)* who stated that the continued high norepinephrine accumulation in the cerebellum with aging reflects active uptake and storage processes and also maintenance of adrenergic neurons with age.

In addition *(30)* observed a stowed catabolism of norepinephrine in the hypothalamus of senescent mice. Similar observations were reported in rats by *(27)* who stated that the turnover rate of norepinephrine was lower in the hypothalamus of old rat and greatest in young rats.

This age-related changes in norepinephrine turen over rate were selective rather than general, and this may clarify the increase of norepinephrine content with age observed in our results. The obtained data in tables (1 & 2) indicated that serotonin content was nonsignificantly decreased at 6 and 12 months old rats, but this decrease became significant at 24 months old rats. Some authors reported a significant decrease of serotonin content in certain brain regions of some aged animals *(24)* .

The present results could be explained by the increase turnover of serotonin in certain brain rgions as judged by increase of 5 - hydroxyindol acetic acid (5 - HIAA), the endproduct of serotonin metabolism which had been reported by *(24)* . This could be a result from either stimulation of serotonin (intra) neuronal metabolism *(31)* or increased monoamine oxidase activity *(24)* . Since serotonin is a substrate for monoamine oxidase A (MAOA) isoenzyme, which in contrast to monoamine oxidase B (MAOB) isoenzyme , is unaltered or even slightly reduced during ageing, the former hypothesis seems to be more probable *(31)* . However, it is noteworthy that serotonin binding sites decreased in the rats and human brain *(24, 32, 33)* .

The obtained data Tables (1 & 2) indicated that serum total cholesterol level was very highly significant increased at 6 , 12 and 24 months old rats. Similar results were noticed in rats by *(34)* and also in humans by *(35)* .

Moreover, the increase in serum total cholesterol with increasing age may also be due to the reduced catabolic rate of serum cholesterol *(36)* or reduced activity of cholesterol 7 α - hydroxylase *(37)* or may be due to impairment of feed back inhibition mechanism of cholesterol synthesis by ageing *(38)* .

Tables (1 & 2) showed that serum HDL-cholesterol concentration was increased significantly at 6 month old rats, followed by very highly significant increase at 12 months old rats, but this increase became insignificant at 24 months old rats.

Decreased levels of HDL-cholesterol in ageing rats was reported *(39)* and also in elderly persons *(40, 41)* . It is well known that esterification of free cholesterol from cells and from other lipoproteins is catalysed by the lecithin-cholesterol acyltransferase (LCAT) enzyme, which is part of the HDL and activated by apolipoprotein A-1 (a P0 A-1). Cholesterol ester generated in the LCAT reaction diffuses into the core of the HDL particles where it

Table (1): Mean values & standard error of blood and brain tissues biochemical parameters in control and aging rats.

Parameters / age	Brain tissues			Serum											Blood
	Dopa-mine µg/ g brain	Norepi-nephrine µg/ g brain	Serotonin µg/g brain	Total cholesterol mg/ dl	HDL cholesterol mg/ dl	LDL cholesterol mg/dl	Triacy glycerols mg/dl	Iron µg/ dl	TIBC µg/ dl	Urea nitrogen mg/dl	Creatinine mg/ dl	Uric acid mg/ dl	unsaturated iron binding capacity	Iron saturation percent	Glucose-6 phophate dehydrogenase mu/ 10^9 RBCS
2 months	1.151± 0.043	0.44± 0.01	1.24± 0.13	57.59± 2.35	24.38± 1.25	18.05± 1.17	74.68± 1.98	251.54± 5.01	375.15± 9.39	31.28± 0.39	0.417± 0.012	1.143± 0.037	123.61± 12.50	67.57± 2.64	239.55± 11.16
6 months	1.106± 0.53	0.54± 0.07	1.14± 0.17	158.03± 9.68***	30.75± 1.87*	108.01± 10.35***	96.43± 3.54**	240.16± 12.54	340.31± 9.41*	32.68± 0.87	0.486± 0.01**	1.233± 0.072	100.15± 15.40	70.98± 4.08	181.94± 7.73***
12 months	0.542± 0.044***	0.54± 0.04*	1.08± 0.07	225.35± 11.75***	36.90± 1.78***	165.01± 11.49	117.21± 6.11***	217.26± 5.84**	332.48± 5.94**	39.82± 1.19***	0.580± 0.02***	1.938± 0.168***	115.22± 9.07	65.58± 2.33	114.25± 2.99***
24 months	0.397± 0.01***	0.82± 0.07***	0.83± 0.05*	285.83± 14.31***	28.23± 3.16	226.19± 14.83***	156.12± 8.62***	190.05± 6.42***	299.49± 7.83***	77.34± 3.57***	1.205± 0.08***	2.831± 0.115***	109.47± 10.81	66.67± 4.32	98.91± 6.15***

* = Significant P < 0.05
** = High significant P < 0.01
*** = Very high signifciant P < 0.001

HDL = high density lipoprotein
LDL = low density lipoprotein
TIBC = Total iron binding capacity

then transported from the tissues to the liver *(42)*. Moreover, the HDL particles isolated from the plasma of aged rats were poor substrates for LCAT enzyme due to a significant decrease in the content of the key HDL apoprotein apo A -1 and a rise in apo E which is an inferior substrate for LCAT enzyme and this may also clarify the decline of HDL - cholesterol levels in aged rats *(39, 43)*.

Tables (1 &2) showed that serum LDL - cholesterol level was very highly significant increased at 6,12 and 24 months old rats. The age-related increase in LDL-cholesterol concentration may be ascribed to the decrease of cellular LDL uptake with age *(44)* and might result from the age related decline in the ability of cells to degrade LDL *(45)* . Our results may also be explained by the decrease in the fractional rate of removal of the lipoproteins from the circulation because of the age-related decline in the LDL receptor activity as the number of LDL receptors per cell decreased *(35, 46)*. Other possible mechanisms by which the receptor mediated fractional rate of catabolism of LDL might decrease with ages including an increasing in the degree of suppression of LDL receptor synthesis that is normally exerted by cellular unesterified cholesterol *(35)* . Tables (1 &2) illustrated that the mean values of serum triacylglyceroles concentrations were highly significant increased at 6 months followed by very highly significant increased at 12 and 24 months old rats *(41)*. Lipoprotein lipase, which hydrolyze triacylglycerols of the plasma lipoproteins, was found to be decreased with advancing age *(3,47)*. Thus , our result could be attributed to the age - related decrease in lipoprotein lipase activity. Our results could also be ascribed to the age - related decline in the removal of triacylglycerols from the plasma as previously demonstrated *(48)* , in that the VLDL - triacylglycerols kinetics indicated that there is a deterioration in the ability of aged rats to remove VLDL triacylglycerols from the plasma , resulting in an increase of plasma triacylglycerols concentration.

The obtained data in tables (1 & 2) demonstrated that serum iron concentration was nonsignificantly decreased at 6 months old rats, while this decrease became highly significant and very highly significant at 12 and 24 months old rats respectively. Our results seem to be similar to those reported in rats *(49)* . Tables (1 & 2) indicated that total iron binding capacity was significantly decreased at 6 months old rats, followed by highly significant decrease at 12 months and very highly significant decrease at 24 months old rats. Similar results to this finding were reported in human *(49)* . Iron deficiency is occasionally a problem with the elderly not only due to poor dietary intake , but also to the decline in the ability of parietal cells to secrete HCL with increasing age . In addition age- associated decreased of gastric acid secretion and decreased mucosal surface area may lead to diminished nutrient uptake , in this connection anaemia may arise in the old ages from both poor iron and vitamin B12 absorption *(3)*.

In addition , vitamin C, which enhances the absorption of dietary nonheme iron was reported to be decreased in the elderly *(50)* . So , the iron decrease in our results may be attributed to either malabsorption of iron or decreased in some factors needed for iron absorption.

Iron is transported in the plasma attached to the specific binding protein (Transferrin), and total iron binding capacity is reduced in protein deficiency *(51)* . Thus , our results concerning the decrease of total iron binding capacity could be attributed to the protein deficiency which was reported in the elderly *(50)* . However, the association of reduced total iron binding capacity with malabsorption of iron in the elderly is due to the accompanying protein deficiency and not to any direct relationship *(51)*. The obtained data in tables (1&2) indicated that blood urea nitrogen concentration was nonsignificantly increased at 6 months old rats . similar results to this finding were reported in rats *(52)* . The authors attributed the increase of blood urea nitrogen levels to the possibility of chronic renal disease associated with ageing. In addition , glomerular function declines with age as the number of functioning glomeruli is reduced *(53)* . This was furtherly explained *(54)* due to progressive loss of functioning cells that do not have the ability to divide and accordingly, nepherons as well as nerve cells are gradually lost with increasing age. There is strong evidence that the protein intake of diet appears to be an important factor in the incidence of nephritis observed in old rats *(55)* . This was partially explained *(54)* as the protein - rich diet induces chronic renal hyperfiltration and hyperfusion and thereby cause

Table (2): Analysis of variance of blood and brain tissues biochemical parametrs in control and aging rats.

Parameters / age	Brain tissues			Serum											Blood
	Dopa-mine µg/ g brain	Norepi-nephrine µg/ g brain	Serotonin µg/g brain	Total cholesterol mg/ dl	HDL cholesterol mg/ dl	LDL cholesterol mg/dl	Triacy glycerols mg/dl	Iron µg/ dl	TIBC µg/ dl	Urea nitrogen mg/dl	Creatinine mg/ dl	Uric acid mg/ dl	unsaturated iron binding capacity	Iron saturation percent	Glucose-6 phophate dehydrogenase mu/ 10^9 RBCS
2 months	1.151[a]	0.44[a]	1.24[a]	57.59[a]	24.38[a]	18.05[a]	74.68[a]	251.54[a]	375.15[a]	31.28[a]	0.417[a]	1.143[a]	123.61	67.57	239.55[a]
6 months	1.106[a]	0.54[a]	1.14[ab]	158.03[b]	30.75[b]	108.01[b]	96.43[b]	240.16[ab]	340.31[b]	32.68[a]	0.486[a]	1.233[a]	100.15	70.98	181.94[b]
12 months	0.542[b]	0.54[a]	1.08[ab]	225.35[c]	36.90[c]	165.01[c]	117.21[c]	217.26[b]	332.48[b]	39.82[b]	0.580[b]	1.938	115.22	65.58	114.25[c]
24 months	0.397[c]	0.82[b]	0.83[b]	285.83[b]	28.23[ab]	226.19[a]	156.12[d]	190.05[c]	299.49[c]	77.34[c]	1.205[c]	2.831[c]	109.47	66.67	98.91[c]

* Values which have different letters are significantly different from each other and vice versa.

progressive glomerular structural damage.

The obtained data in tables (1 &2) showed a highly significant increase of serum creatinine concentration at 6 months old rats, followed by very highly significant increase at 12 and 24 months old rats.

Similarly , a significant decline in renal creatinine excretion with increasing age was reported by *(56)* . In addtion , highly significant reduction in creatinine clearance with advancing age due to the decline in glomerular filtration rate was also reported *(56, 57)*.. Creatinine reabsorption during low renal blood flow is thought to result from its passive back diffusion from the lumen to the blood . Thus , when renal blood flow is low , passive reabsorption of creatinine might result in a lower creatinine clearance and a high serum creatinine concentration *(56)*.

The obtained data in tables (1 &2) showed a nonsignificant increase of serum uric acid concentration at 6 months old rats, followed by very highly significant increase at 12 and 24 months old rats.

The elevation of serum uric acid concentration with increasing age that observed in this work could be due to the partial impairment of renal function *(58)* and / or increased production of uric acid from tissue nucleoprotein with increasing age *(59)*.

The obtained data in table (1 & 2) showed a very highly significant decrease of glucose -6- phosphate dehydrogenase activity in erythrocytes at 6 , 12 and 24 months old rats.

Similar results to this findings were demonstrated in human erythrocytes *(60)* as well as in rat erythrocytes *(61)* . Moreover, the cells became senescent, they grow much more slowly and make less protein than the younger ones *(62)*. Our result could be attributed to the accumulation of altered forms of glucose-6- phosphate dehydrogenase enzyme in the aged cells *(63)* . The authors revealed their observations due to the presence of altered enzyme molecules which differ from the normal molecules in structure and function . In addition , altered glucose -6- phosphate dehydrogenase is likely to generate less amount of $NADPH+H^+$ than normal enzyme and hence decrease the level of reduced glutathione *(64)*.

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الملخص العربى

بعض الدراسات البيوكيميائية على دم ونسيج المخ فى الفئران ذات الأعمار المختلفة

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أجريت هذه الدراسة على عدد ٨٠ فأراً من الذكور ، وقد قسمت هذه الفئران طبقاً للعمر إلي أربع مجموعات رئيسية كل منها تحتوى على عدد عشرين فأراً وهى كالتالى :

١ - المجموعة الأولى : تبلغ من العمر شهرين وتمثل الفئران الصغيرة فى السن وتم استخدامها كمجموعة ضابطة

٢ - المجموعة الثانية: تبلغ من العمر ستة أشهر ، وتمثل الفئران فى سن البلوغ .

٣ - المجموعة الثالثة : وتبلغ من العمر إثنا عشرة شهراً وتمثل الفئران المتقدمة فى السن .

٤ - المجموعة الرابعة : تبلغ من العمر أربع وعشرين شهراً وتمثل الفئران المتقدمة جداً فى السن .

تم تقسيم كل مجموعة رئيسية إلى مجموعتين فرعيتين تحتوى كل منهما على عدد عشرة فئران . استخدمت المجموعة الفرعية الأولى لقياس تركيز الدوبامين ، النور ادرينالين والسيرتونين فى المخ كما تم استخدام المجموعة الفرعية الثانية لقياس بعض المكونات الكيميائية فى الدم مثل نشاط إنزيم جلوكوز -٦- فوسفات ديهيدروجينيز فى كرات الدم الحمراء ، أما فى المصل فقد تم قياس الكولسترول الكلى ، الكولسترول فى البروتينات الذهنية عالية الكثافة الكولسترول فى البروتينات الذهنية منخفضة الكثافة، الجلسريدات الثلاثية ،الحديد ، سعة إرتباط الحديد الكلية ، اليوريا، الكرياتينين وحمض اليوليك .

ويمكن تلخيص نتائج هذه الدراسة فيما يلى :

أظهرت النتائج إنخفاض غير معنوى لتركيز الدوبامين والسيروتونين فى نسيج المخ وكذلك لمستوى الحديد فى المصل عند عمر ٦ شهور متبوعاً بأنخفاض معنوى عالى وأخر معنوى عالى جداً عند الأعمار ١٢ ، ٢٤ شهراً على التوالى .

كما سجلت النتائج زيادة غير معنوية لتركيز النورادرينالين فى المخ وكذلك تركيز كل من اليوريا وحمض اليوليك فى المصل عند عمر ٦ شهور متبوعاً بزيادة معنوية عالية وعالية جداً عند عمر ١٢ ، ٢٤ شهراً على التوالى فى تركيز كلاً من الكوليسترول الكلى، مستوى الكوليسترول فى البروتينات الذهنية عالية الكثافة والكوليسترول فى البروتينات الذهنية منخفضة الكثافة وتركيز الجلسريدات الثلاثية وكذلك الكرياتينين فى المصل .

مما سبق يتضح تأثير مراحل العمر المتقدمة على مكونات الدم ونسيج المخ وخاصة الدهون والكوليسترول بأنواعة المختلفة ووظائف الكلى ، الأمر الذى يتطلب تنظيم الغذاء لكبار السن حتى يمكن السيطرة على الحالات المرضية التى تصاحب التقدم فى العمر فى الإنسان وحيوانات التجارب .