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Possible Involvement of Dehydroepiandrosterone and Cyproterone Acetate Central Role in Young and Aged Male Rats Fed on High Fat Diet

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The present study aims to investigate the effects of dehydroepiandrosterone (DHEA) and Cyproterone Acetate (CA) on the levels of monoamine neurotransmitters in the brain as well as on the levels of serum DHEA, testosterone and corticosterone in young and aged rats fed on high fat diet. These neurotransmitters and hormones were chosen because of their association with obesity, mood and cognitive functions. Young and aged male rats were divided into two normal basal diet and high fat diet fed groups. Each group was further divided into control, DHEA, CA and DHEA+CA. Treatments were given for either 2 or 8 consecutive weeks. DHEA treatment induced a significant reduction in the cortical contents of norepinephrine, epinephrine, dopamine and serotonin in aged rats, whereas young rats fed on a normal diet exhibited a significant elevation in serotonin level. Young rats fed on high fat diet exhibited a significant elevation of both norepinephrine and epinephrine. CA treatment induced an increase in cortical monoamine levels of young and aged rats fed on both types of diet. All treatments increased hypothalamic serotonin contents. DHEA treatment increased serum DHEA, corticosterone and testosterone levels, while CA treatment decreased corticosterone and testosterone levels without significance on the DHEA level in all treated groups. Treatment with DHEA+CA restored testosterone to its normal value. In general, there is a positive correlation between serum DHEA level and hypothalamic neurotransmitters and the levels of studied serum hormones. On the other hand, there was a negative correlation between serum DHEA level and cortical neurotransmitters. It is possible that DHEA induces its hypolipidemic action through stimulating the hypothalamic pituitary adrenal axis resulting in elevating corticosterone level with its known lipolytic action. The young rats fed on high fat diet were the most affected group as the diet caused inverse results in correlation between serum DHEA level and hypothalamic monoamine neurotransmitters and these results might have led to discourage the obesity, mood and cognitive functions. Also, treatment with the two drugs together would maintain normal levels of DHEA, corticosterone and testosterone.

Key words: Dehydroepiandrosterone, cyproterone acetate, monoamines, corticosterone, testosterone

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INTRODUCTION

Dehydroepiandrosterone DHEA was a weak androgen naturally occurring C_{19} steroid. It was secreted from retecularis cells of the adrenal gland and could be detected in relatively high concentrations in the blood of young humans but these levels gradually decreased to approximately 10% by the age of 80 (Orentreich *et al*., 1984). It was present in low concentration in the peripheral circulation of adult mammals of both sexes (Imai *et al*., 1999). DHEA was also synthesized in the brain by the neurons and astrocytes (Leskiewicz *et al*., 2006). For this reason DHEA and similar steroid molecules had been named neurosteroids.

The effect of DHEA had been studied in obese rats where it reduced the adiposity of nearly all models of rodent obesity (Cleary, 1991). Therefore, it was possible that one mechanism by which DHEA may exert its beneficial effects was by regulation of food intake (Catalina *et al*., 1999), alternatively, a reduction in protein digestibility in the short term and a protective effect on body protein with a selective mass loss from body fat had also been suggested (De Heredia *et al*., 2007).

The antiandrogenic and gestagenic steroid Cyproterone Acetate (CA) had been widely used in treatment of hyperandrogenic alopecia (Carmina and Lobo, 2003), prostatic cancer (Gurina *et al*., 2003) and acne (Purdy and Berker, 2006). There was currently a debate about the safety of CA and some reports suggested its effects in rat liver and human hepatocytes (Kasper, 2001). CA induced a significant decrease in the body weight and liver/body weight ratio and increased liver oxidative stress as appeared in the earlier study (Abo-Nour *et al*., 2005).

In the present study young rats of 2 months age were used as the density of innervation and the topography of the rat brain cortex was then established (Kalsbeek *et al*., 1988). Eight months old rats were used as early signs of the ageing process (decrease in the synapses of noradrenergic neurons in the frontal cortex) appeared at that age (Ishida *et al*., 2001). This study aimed at exploring some of DHEA's favorable effects on obesity through the complicated physiologic pathways might be based upon its action as an antiglucocorticoid. An additional objective was to highlight the difference in the DHEA hormonal effect in normal young and aged rats and to explore the impact of high fat-diet. Finally, the possible perturbations in the central neurotransmitters levels related to changes in serum levels of corticosterone, testosterone and DHEA were also studied.

MATERIALS AND METHODS

Animals: Two hundred twenty four adult male Wistar rats were obtained from the Egyptian Institution of Serum and Vaccine (Helwan) and were divided in 2 groups. The first one was referred to as young (2 months old rats, n = 112) and the other half as aged (8 months old rats, n = 112). The animals were kept under controlled temperature of 25±2°C and 12 h light/12 h dark cycle throughout the experiment. A commercial pelleted diet and fresh vegetables were used before the experiment. The animals were allowed to adapt to the laboratory conditions for two weeks before the beginning of the experiment. Water and food were available *ad libitum*.

Diets: Two different diet compositions were used in this experiment, a normal balanced control diet (20% protein, 15% fat and 65% carbohydrates) and a high fat control diet (20% protein, 45% fat and 35% carbohydrates). The compositions of these diets were formulated according to Baker *et al*. (1979), Tagliaferro *et al*. (1995) and Abadie *et al*. (2001).

Chemicals: Cyproterone acetate ($C_{24}H_{29}ClO_4$) (CA) was supplied by Schering, Germany (LOT. No. 481A) and suspended evenly in propylene glycol and i.p. injected as 0.1 mL/100 g b.wt.

Dehydroepiandrosterone ($C_{19}H_{28}O_2$) (DHEA) purchased from Action labs Inc., Long Island, NY (Batch No. 646LE). Suspended evenly in propylene glycol and i.p. injected as 0.1 mL/100 g b.wt.

Experimental design: The animal experiments were conducted in Zoology Department animal house in the college for Women, Arts, Sciences and Education, Ain Shams University and the laboratory works were conducted in physiology lab. of National Organization for Drug Control and Research (NODCAR).

The animals were divided into two main groups young (2 weeks old) and aged (8 weeks) each group contained 112 rats which were then divided into two subgroups, one was maintained on the normal balanced control diet, whereas the other was maintained on a high fat diet. Each of these two groups was further subdivided into four subgroups; each one contained 14 rats as follows:

- Control subgroup, which received 0.1 mL/100 g b.wt. of the propylene glycol vehicle
- DHEA group received 25 mg/kg/day DHEA
- CA group, received 10 mg/kg/day CA

- DHEA+CA group which received 25 mg/kg/day DHEA+10 mg/kg/day CA

All groups were injected (i.p.) for either two or eight consecutive weeks from the beginning of the experiment. The aforementioned doses were equivalent to human daily dose and calculated according to Paget and Barnes (1964).

Following the completion of the experiments, the rats were sacrificed after 12 h from the last dose by rapid decapitation. Core Blood samples were collected after decapitation in glass tubes and centrifuged, then serum was separated and subjected to the methods of Glass and Johnson (1993), Ling and Jamali (2003) and Gonzalo-Lumbreras *et al.* (2003) for the determination of serum testosterone, DHEA and corticosterone concentrations, respectively, by High Performance Liquid Chromatography (HPLC). Brain was excised and dissected immediately on ice according to Palkovits and Brownstein (1988). The frontal cerebral cortex and the hypothalamus were separated, weighed and used for the assay of monoamines by HPLC according to the method of Pagel *et al.* (2000).

Statistical analysis: Statistical analysis was evaluated by one-way ANOVA. Once a significant F-test was obtained, LSD comparisons were performed to assess the significance of differences among various treatment groups. Statistical Processor System Support SPSS for Windows software, Release 14.0 (SPSS, Chicago, IL) was used. Also, correlation was obtained between serum DHEA level and cortical and hypothalamic monoamine neurotransmitters and between serum DHEA level and serum corticosterone and testosterone level in all groups and in young and aged groups divided according to diet and treatment using the same statistics package.

RESULTS AND DISCUSSION

The DHEA injection caused as compared to control value, a significant reduction in the cortex monoamine neurotransmitters level of aged normal diet-fed rats during the experimental period, but the young-rat group showed only significant elevation of serotonin level after eight weeks of DHEA treatment. On the contrary, the high fat diet-fed rats exhibited significant elevation of both norepinephrine and epinephrine in the aged group, but serotonin only was affected in the young group. CA treatment for 8 weeks caused an increase in the brain cortex monoamines contents in all groups except in young high fat diet-fed rats there was a reduction in serotonin level as compared to control value. Co-treatment with DHEA and CA showed an increase in the level of cortical monoamines in all treated groups as compared to control (Table 1).

On the contrary to the results of the brain cortex DHEA treated rats showed a significant elevation in the hypothalamic content of monoamines in both diets, except a significant reduction in the dopamine content in young normally fed rats and senile fat diet fed rats (Table 2). CA treatment caused a significant elevation of monoamines content in all treated groups after 8 weeks of treatment, except in epinephrine and dopamine contents

Table 1: Effect of dehydroepiandrosterone DHEA and/or Cyproterone Acetate (CA) on the brain cortical monoamine contents (ng mg^{-1}) of young and aged male rats

			Groups							
			Normal diet				High fat diet			
Parameters	Ages	Time (weeks)	Control	DHEA	CA	DHEA +CA	Control	DHEA	CA	DHEA+CA
Norepinephrine	Young	2	0.76±0.07	0.56±0.07	1.17±0.09^{ab}	1.60±0.12^{abc}	0.70±0.07	0.88±0.08	1.05±0.02^{a}	1.01±0.07^{a}
		8	1.16±0.14	1.20±0.03	1.44±0.04	1.59±0.17^{ab}	0.79±0.05	0.91±0.07	0.91±0.06	1.13±0.10^{a}
	Aged	2	1.47±0.16	0.99±0.09^{a}	1.39±0.12^{b}	1.04±0.08^{ac}	1.08±0.06	0.99±0.14	1.67±0.16^{ab}	0.69±0.05^{abc}
		8	1.83±0.09	0.88±0.06^{a}	2.32±0.12^{ab}	2.02±0.10^{bc}	1.39±0.11	1.73±0.16^{a}	1.78±0.09^{a}	2.00±0.12^{a}
Epinephrine	Young	2	0.76±0.08	0.52±0.08	1.11±0.09^{ab}	1.50±0.12^{abc}	0.53±0.06	0.81±0.08^{a}	0.98±0.04^{a}	0.68±0.06^{c}
		8	1.11±0.15	1.22±0.03	1.53±0.04^{ab}	1.64±0.15^{ab}	0.77±0.05	0.91±0.07	0.83±0.07	0.98±0.09
	Aged	2	1.07±0.13	0.57±0.07^{a}	0.80±0.12	0.52±0.05^{ac}	0.49±0.04	0.52±0.07	1.95±0.09^{ab}	1.20±0.09^{abc}
		8	1.91±0.14	0.85±0.06^{a}	2.47±0.15^{ab}	2.00±0.10^{bc}	1.35±0.09	1.75±0.19^{a}	1.70±0.11^{a}	2.11±0.11^{abc}
Dopamine	Young	2	0.91±0.06	0.59±0.08	0.12±0.10^{a}	1.75±0.13^{abc}	0.90±0.07	0.79±0.06	1.17±0.02	3.06±0.34^{abc}
		8	1.64±0.21	1.66±0.04	2.09±0.05	2.18±0.17^{ab}	1.19±0.09	1.24±0.13	1.67±0.12^{a}	1.72±0.14^{ab}
	Aged	2	4.31±0.14	3.17±0.31^{a}	4.05±0.35^{b}	4.52±0.33^{b}	2.60±0.20	2.35±0.11	3.44±0.25^{ab}	2.09±0.15^{c}
		8	1.87±0.13	0.98±0.06^{a}	2.85±0.15^{ab}	2.17±0.11^{bc}	1.69±0.13	2.12±0.22	2.20±0.14^{a}	2.64±0.16^{ab}
Serotonin	Young	2	0.10±0.01	0.15±0.012	0.16±0.002	0.06±0.002	0.08±0.005	0.16±0.017	0.22±0.004^{a}	0.18±0.016
		8	0.42±0.03	0.53±0.01^{a}	0.80±0.03^{ab}	0.70±0.04^{ab}	0.21±0.01	0.58±0.05^{a}	0.35±0.02^{ab}	0.39±0.03^{ab}
	Aged	2	0.38±0.04	0.25±0.01^{a}	0.27±0.03^{a}	0.25±0.06^{a}	0.13±0.01	0.23±0.04	0.35±0.01^{ab}	0.14±0.01^{c}
		8	0.96±0.08	0.44±0.04^{a}	0.93±0.08^{b}	1.00±0.03^{b}	0.64±0.07	0.61±0.07	0.81±0.05^{ab}	0.88±0.06^{ab}

The results are presented as Mean±SE of 7 rats; Significance at 0.05 level; ^{a}Significant change from the corresponding control value; ^{b}Significant change from the DHEA treated group; ^{c}Significant change from the cyproterone acetate treated group

Table 2: Effect of dehydroepiandrosterone DHEA and/or Cyproterone Acetate (CA) on the brain hypothalamus monoamine contents (ng mg^{-1}) of young and aged male rats

			Groups							
			Normal diet				High fat diet			
Parameters	Ages	Time (weeks)	Control	DHEA	CA	DHEA +CA	Control	DHEA	CA	DHEA+CA
Norepinephrine	Young	2	0.28±0.02	0.29±0.02	0.43±0.04^{ab}	0.28±0.03^{c}	0.28±0.01	0.34±0.02^{a}	0.38±0.03^{a}	0.33±0.01
		8	0.18±0.008	0.15±0.013	0.25±0.02^{ab}	0.33±0.01^{abc}	0.14±0.01	0.21±0.006	0.17±0.007	0.18±0.01
	Aged	2	0.26±0.01	0.50±0.01^{a}	0.21±0.01^{b}	0.14±0.014^{abc}	0.39±0.02	0.44±0.02	0.31±0.01^{ab}	0.37±0.03^{bc}
		8	0.15±0.004	0.24±0.01^{a}	0.25±0.02^{a}	0.16±0.007^{bc}	0.39±0.09	0.23±0.01^{a}	0.33±0.01^{b}	0.18±0.004^{ac}
Epinephrine	Young	2	0.19±0.015	0.19±0.013	0.42±0.04^{ab}	0.49±0.04^{abc}	0.21±0.01	0.34±0.02^{a}	0.41±0.03^{ab}	0.33±0.01^{ac}
		8	0.11±0.01	0.12±0.004	0.06±0.005^{ab}	0.25±0.01^{abc}	0.12±0.01	0.15±0.01	0.08±0.004^{b}	0.14±0.006^{c}
	Aged	2	0.17±0.02	0.42±0.01^{a}	0.17±0.005^{b}	0.43±0.03^{ac}	0.33±0.01	0.27±0.02^{a}	0.23±0.007^{a}	0.24±0.02^{a}
		8	0.13±0.01	0.22±0.01^{a}	0.25±0.02^{a}	0.14±0.015^{bc}	0.17±0.01	0.17±0.03	0.27±0.01^{ab}	0.12±0.006^{c}
Dopamine	Young	2	0.35±0.03	0.37±0.03	0.59±0.04^{ab}	0.67±0.03^{abc}	0.43±0.03	0.52±0.04^{a}	0.50±0.03	0.48±0.01
		8	0.26±0.01	0.17±0.01^{a}	0.13±0.01^{a}	0.36±0.03^{abc}	0.10±0.003	0.17±0.02	0.07±0.005^{b}	0.09±0.005^{b}
	Aged	2	0.77±0.06	1.81±0.04^{a}	0.68±0.03^{ab}	0.24±0.02^{abc}	0.49±0.01	0.63±0.06^{a}	0.37±0.01^{ab}	0.43±0.02^{b}
		8	0.24±0.02	0.32±0.02^{a}	0.34±0.03^{a}	0.21±0.02^{bc}	0.23±0.01	0.28±0.01	0.45±0.02^{ab}	0.21±0.006^{bc}
Serotonin	Young	2	0.08±0.006	0.10±0.004^{a}	0.13±0.005^{ab}	0.13±0.005^{ab}	0.06±0.003	0.12±0.005^{a}	0.13±0.007^{a}	0.08±0.002^{abc}
		8	0.02±0.003	0.04±0.003	0.04±0.004^{a}	0.11±0.006^{abc}	0.04±0.003	0.062±0.02^{a}	0.057±0.005	0.12±0.004^{abc}
	Aged	2	0.12±0.006	0.28±0.005^{a}	0.11±0.005^{b}	0.07±0.009^{abc}	0.13±0.008	0.20±0.005^{a}	0.13±0.007^{b}	0.14±0.01^{b}
		8	0.06±0.007	0.06±0.005	0.06±0.003	0.03±0.003^{abc}	0.03±0.004	0.09±0.008^{a}	0.08±0.002^{a}	0.05±0.002^{abc}

The results are presented as Mean±SE of 7 rats; Significance at 0.05 level; ^{a}Significant change from the corresponding control value; ^{b}Significant change from the DHEA treated group; ^{c}Significant change from the cyproterone acetate treated group

Table 3: Effect of dehydroepiandrosterone DHEA and/or Cyproterone Acetate (CA) on serum DHEA (ng mL^{-1}), corticosterone (ng mL^{-1}) and testosterone of young and aged male rats

			Groups							
			Normal diet				High fat diet			
Parameters	Ages	Time (weeks)	Control	DHEA	CA	DHEA +CA	Control	DHEA	CA	DHEA+CA
DHEA	Young	2	2.43±0.17	2.47±0.36	2.18±0.16	2.40±0.20	1.87±0.18	2.10±0.13	1.49±0.10^{b}	1.0±0.07^{abc}
		8	1.66±0.22	2.30±0.14^{a}	1.51±0.11^{b}	2.09±0.08^{c}	2.00±0.13	2.89±0.20^{a}	2.01±0.13^{b}	2.07±0.14^{b}
	Aged	2	2.31±0.18	3.31±0.23^{a}	2.36±0.24^{b}	2.41±0.16^{b}	2.40±0.20	3.15±0.17^{a}	2.99±0.24^{a}	3.09±0.21^{a}
		8	1.50±0.07	3.12±0.17^{a}	1.24±0.09^{b}	1.73±0.10^{bc}	1.66±0.11	2.41±0.16^{a}	1.39±0.10^{b}	2.08±0.12^{c}
Corticosterone	Young	2	134.30±5.7	138.30±11.5	80.00±6.6^{ab}	61.00±3.3^{ab}	110.10±11.1	270.00±14.5^{a}	56.00±3.3^{ab}	87.40±7.3^{bc}
		8	126.60±9.0	124.00±6.8	63.70±3.4^{ab}	79.60±7.4^{ab}	65.90±5.3	123.90±5.7^{a}	55.40±5.1^{b}	72.00±5.5^{b}
	Aged	2	129.90±10.2	174.30±15.9^{a}	85.70±6.8^{ab}	117.10±11.5^{bc}	71.10±6.9	138.90±13.2^{a}	68.00±6.2^{b}	79.40±6.4^{b}
		8	148.00±8.8	176.90±8.4^{a}	38.90±2.6^{ab}	59.40±5.2^{ab}	87.60±5.6	113.40±11.2^{a}	54.60±5.0^{ab}	70.60±5.6^{b}
Testosterone	Young	2	35.60±2.9	51.20±3.8^{a}	15.80±1.3^{ab}	34.80±3.6^{bc}	28.90±2.3	40.20±3.3^{a}	24.60±2.6^{b}	31.80±3.6
		8	36.80±1.5	57.70±1.6^{a}	17.30±0.6^{ab}	35.60±7.2^{bc}	61.00±2.7	110.00±6.0^{a}	36.70±3.7^{ab}	35.80±2.8^{ab}
	Aged	2	24.70±2.7	99.10±6.0^{a}	8.50±0.5^{ab}	20.00±2.0^{bc}	21.70±2.3	36.00±3.3^{a}	18.70±2.0^{b}	15.20±1.3^{b}
		8	37.20±1.9	75.40±5.2^{a}	24.10±3.4$^{a\,b}$	38.60±2.6^{bc}	35.30±1.6	66.60±4.4^{a}	19.90±1.0^{ab}	27.60±2.2^{b}

The results are presented as Mean±SE of 7 rats; Significance at 0.05 level; ^{a}Significant change from the corresponding control value; ^{b}Significant change from the DHEA treated group; ^{c}Significant change from the cyproterone acetate treated group

in the young normal or high fat diet-fed rats where the level decreased significantly. DHEA+CA treatments caused significant elevation of the monoamines levels except dopamine after 8 weeks of treatment in young rats fed on high fat diet as compared with the control values. The aged rats treated with DHEA+CA demonstrated a reduction in the monoamines levels after the experimental period in all treated groups as compared to the corresponding control values, except for a significant elevation in the serotonin level of aged rats fed on high fat diet.

Rats treated with DHEA exhibited a significant increase in DHEA, corticosterone and testosterone levels as compared to the control levels (Table 3). In contrast, CA treatment caused a significant reduction in corticosterone and testosterone levels concomitant with a slight, but not significant decrease in DHEA level in all treated groups. DHEA+CA treatment caused a significant reduction in corticosterone and testosterone levels, respectively, as compared to control value in young and aged normally fed groups as well as in the young high fat diet-fed group.

Table 4 shows the correlation between serum DHEA level and serum corticosterone and testosterone levels on one hand and the cortical and hypothalamic monoamine neurotransmitters on the other hand. In general, in all groups there was positive correlation between DHEA and serum testosterone level $r = 0.34$, $p<0.001$ (Fig. 1) and between DHEA with serum corticosterone $r = 0.33$, $p<0.001$ and DHEA with hypothalamic dopamine $r = 0.32$,

Table 4: Pearson's correlation between the DHEA level and brain monoamine neurotransmitters and serum hormones under investigation for all groups

Variables	All groups	Young		Aged		DHEA		CA		DHEA+CA	
		Normal diet	High fat diet	Normal diet	High fat diet	Young	Aged	Young	Aged	Young	Aged
Serum											
Corticosterone	0.33***	-	0.28*	0.65***	0.35**	-0.41*	0.55**	0.64***	-	-	0.52**
Testosterone	0.34***	-	0.72***	0.63***	-	0.44*	-	-	-	-	-0.66***
Cortex											
Dopamine	-	-0.27*	-0.40**	-	-	-	-	-0.43*	0.38*	-0.60**	-
Serotonin	-0.31***	-0.38**	0.55***	-0.64***	-0.62***	-	-0.54**	-0.39*	-0.63***	-	-0.70***
Epinephrine	-0.24***	-	-	-0.69***	-0.46***	-	-0.50**	-	-	0.66***	-0.47*
Norepinephrine	-0.26***	-	-	-0.70***	-0.33*	-	-	-	-0.47*	0.42*	-0.75***
Hypothalamus											
Dopamine	0.32***	0.30*	-0.42**	0.55***	0.37**	-	0.41*	-	-	-	0.70***
Serotonin	0.45***	0.37**	-	0.53***	0.66***	-	-	-	0.88***	0.82***	0.70***
Epinephrine	-	-	-0.37**	0.51***	-	-	0.45*	-	-	-	-
Norepinephrine	0.16*	0.27*	-0.42**	0.42**	-	-	0.41*	-	-	-	0.61**

-: Insignificant correlation; *p<0.05; **p<0.01 and ***p<0.001

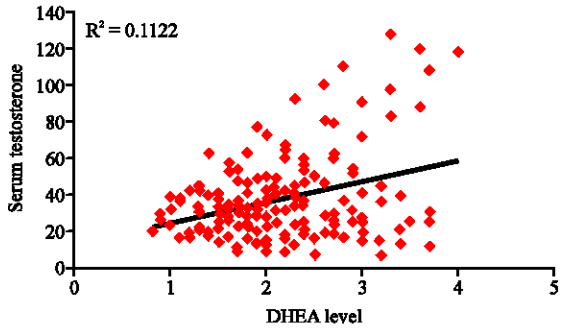

Fig. 1: Regression between serum DHEA level and serum testosterone

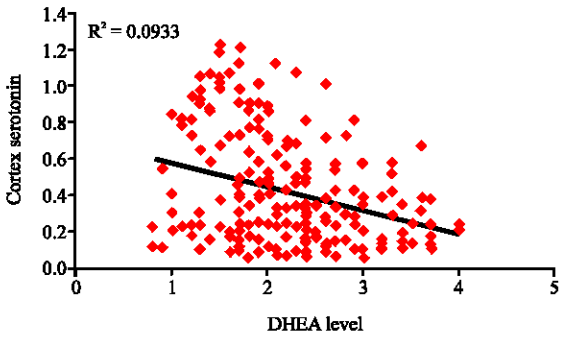

Fig. 2: Regression between serum DHEA level and the cortex serotonin

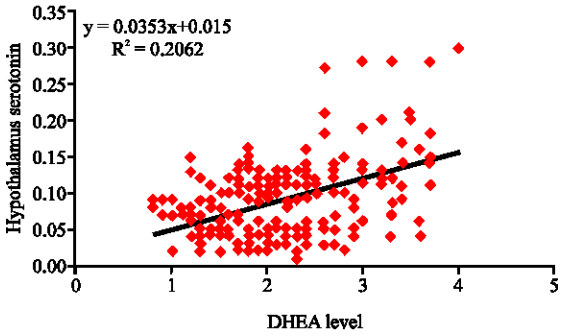

Fig. 3: Regression between serum DHEA level and hypothalamus serotonin

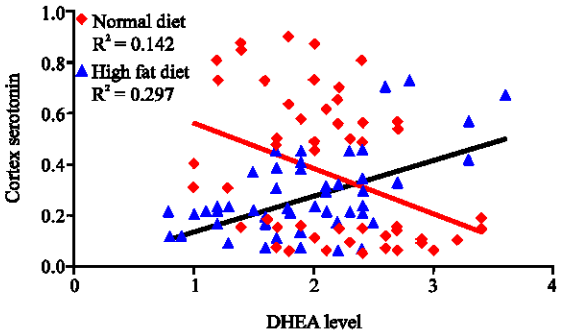

Fig. 4: Regression between serum DHEA level and cortex serotonin in young rats

p<0.001 and serotonin r = 0.45, p<0.001. In contrast, a negative correlation was recorded between DHEA with cortical monoamine neurotransmitters (serotonin r = -0.31, p<0.001), (epinephrine r = -0.24, p<0.001), (norepinephrine r = -0.26, p<0.001). Figure 2 and 3 show the general correlation between DHEA serum level and cortical or hypothalamic serotonin level. Figure 4-7 demonstrated the correlation between DHEA level and cortex and hypothalamus serotonin in young and aged rats divided according to diet. The correlation between DHEA level and cortex serotonin in young rats fed on normal fat diet was negative r = -0.38, p<0.01, however, young rats fed on high fat diet showed a positive correlation r = 0.55 p<0.001. The significant positive correlation was reported between DHEA level and hypothalamus serotonin in aged rats and young rats fed on normal diet, while young rats fed on high fat diet exhibited a non-significant correlation. Also, young rats fed on high fat diet showed a negative correlation with other hypothalamic monoamines. In young rats fed on high fat diet, correlation between

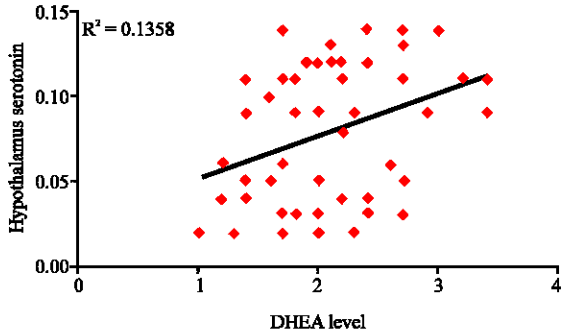

Fig. 5: Regression between serum DHEA level and hypothlamus serotonin in young rats fed on normal diet

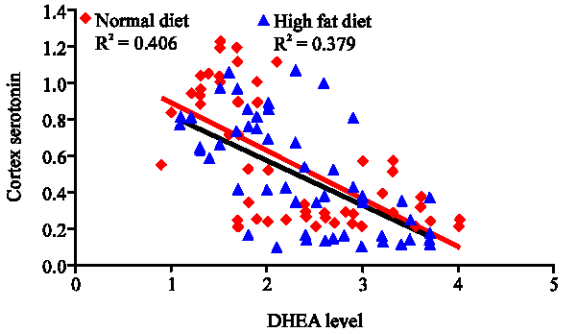

Fig. 6: Regression between serum DHEA level and cortex serotonin in aged rats

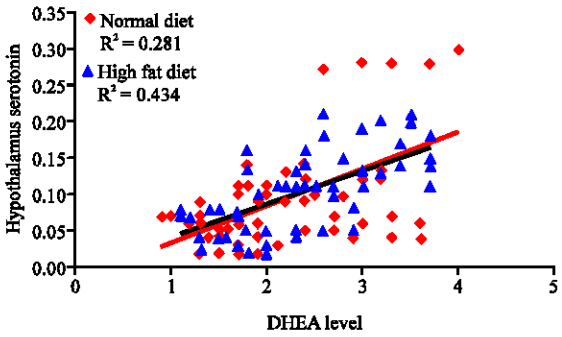

Fig. 7: Regression between serum DHEA level and hypothalamus serotonin in aged rats

DHEA and serum testosterone level was increased r = 0.72, p<0.001, while a negative correlation r = -0.42, p<0.001 was reported between serum DHEA and cortex dopamine (Fig. 8).

Certain brain cortex areas may contribute to a propensity for obesity such as the dorsolateral prefrontal cortex known to be implicated in the inhibition of inappropriate behavior, satiety and meal termination (Le *et al*., 2006; Souza *et al*., 2007). The present results support the antiobisity effect through the reverse of the

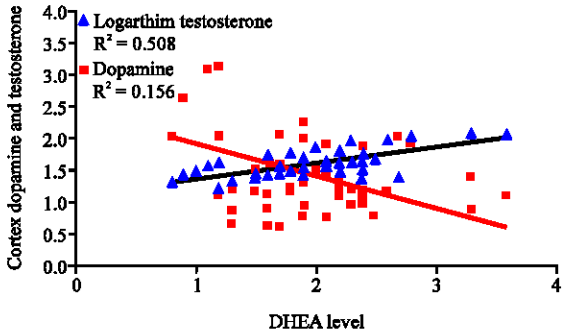

Fig. 8: Regression between serum DHEA level and cortex dopamine and testosterone in young rats fed on normal diet

reduced concentrate of serotonin in obese group which was revealed by the positive correlation between DHEA level and cortex serotonin in high fat diet fed young rats (Wright *et al*., 1995).

Numerous studies implicate the hypothalamus as an important region in controlling food intake and summarized evidence demonstrating that, in the rat, hypothalamic serotonin and dopamine are the major feeding inhibitory neurotransmitters, although both norepinephrine and epinephrine occasionally may have the same effect (Leibowitz, 1987; Leibowitz *et al*., 1990; Amer *et al*., 2004). Consequently, the elevation of monoamines in the hypothalamus advocated the hypothesis that DHEA might decrease food intake particularly in fat subjects. In support of this interpretation the earlier reports showing that DHEA by itself induced some changes in serotonin receptor (5-HIAA) in the obese satiated model (Catalina *et al*., 2001; Porter *et al*., 2005). Moreover, the anxiolytic effect of DHEA administration, previously demonstrated by Imamura and Prasad (1998), Falkenstein *et al*. (2000) and Navar *et al*. (2006) might have had additive effect through the hypothalamic-centered mechanisms. In addition to relevant to mood and neurodegenerative disorders (Pérez-Neri *et al*., 2008).

Meriggiola *et al*. (1996) detected in subjects treated with CA, a tendency for a decrease in body weight. The significant elevation in serotonin levels after CA treatment observed herein correlates with the decrease in body weight of treated animals is consistent with a body of references that point to the participation of serotonin in food intake regulation. In this regard changes in serotonin level have been implicated as modulator of feeding behavior and body weight gain (Leibowitz *et al*., 1990; Amer *et al*., 2004). Moreover, sustaining the central effect of CA and DHEA as the hypophagic effect induced by serotonin requires activation of 5-HT1A and 5-HT1B

receptors and the specific contribution of these subtype receptors is different, since the 5-HT1A subtype showed higher behavioral selectivity (Mancilla-Diaz *et al*., 2005).

Both DHEA and CA treatment induced hypolipidemic action as shown in the earlier study (Abo-Nour *et al*., 2005) and by direct effects on hypothalamic monoamine neurotransmitters this result was supported by the correlation results in different young and aged treated groups and in normal and high fat diet young and aged rats. The young rats fed on high fat diet were the most affected groups as the diet caused inverse results in correlation between serum DHEA level and hypothalamic monoamine neurotransmitters (this means that the treatments induced a hypolipidemic action because the increase in monoamine contents, especially serotonin, in hypothalamus was related with decrease satiety (Leibowitz *et al*., 1990; Porter *et al*., 2005). However, with regard to drug treatments, aged rats treated with CA had the highest correlation value between serum DHEA level and hypothalamic serotonin (r = 0.88) followed by DHEA+CA young rats (r = 0.82) and finally DHEA+CA aged rats (r = 0.70).

Cyproterone acetate had powerful inhibitory effects on androgen action although it also inhibited gonadotropin release (Neumann, 1987). The results (the decreased level of testosterone and corticosterone) obtained with cyproterone acetate treatment may be explained by CA classic antiandrogenic property. It was described by the significant reduction of testosterone and corticosterone levels in all treated groups (in agreement with Shiro (1982) and Meriggiola *et al*. (2003)).

The second possible explanation for CA-induced effects might be through the increased in availability of the monoamines in cortex and hypothalamus tissues which in line with the results of Eaton *et al*. (1999) described the suppression of monoamine oxidase enzyme.

The effect of CA on the brain cortex neurotransmitters may support the earlier studies demonstrating that the largest forebrain target for androgen action as well as the main hypothalamic and limbic centers (DonCarlos *et al*., 2006). CA treatment in young normal or high fat- diet fed lowered the hypothalamic content of dopamine an effect accompanied with a reduction of corticosterone and testosterone levels in the aforementioned treated groups. These effects reflect the disturbed effect on hormones of CA in young male rat (Sabry *et al*., 2000; Ben-Jonathan and Hnasko, 2001).

The CA or DHEA+CA treated groups showed a slight but not significant change in DHEA serum level which may be related to the dose level being lower than previously reported effective ones (Huang *et al*., 1985) or explained by the rapid metabolism of DHEA to other androgenic hormones to replenish the anti-androgenic effect of CA.

DHEA secreted by the adrenal glands represents an appreciable source for the biosynthesis of testicular testosterone and dehydrotestosterone. In addition, a previous study on the interaction of DHEA and glucocorticoids suggested that these two hormones might be competitive for the same intracellular receptor (Charalampopoulos *et al*., 2006).

The present results demonstrated an increase in serum DHEA level in DHEA-treated rats. In agreement with these results, Kimura *et al*. (1998) and Tummala and Svec (1999) recorded that serum DHEA level was increased in rats after treatment with DHEA. Also, Aragno *et al*. (2002) recorded that DHEA treatment in rats induced a significant and dose dependent increase in serum and plasma DHEA levels as compared to the control. The results in the present study are in accordance with those of Gobbi *et al*. (2003) and Rhoden *et al*. (2003) which reported high concentrations of serum total testosterone and DHEAS in the rats treated with DHEA. On the other hand, McIntosh *et al*. (1999) found that testosterone was not significantly affected by DHEA treatment, although there was a tendency for an insignificant increase. In addition, there is a significant elevation of serum corticosterone level in DHEA treated rats. In agreement with Hu *et al*. (2000), who postulated that DHEA, by direct displacement of corticosterone from glucocorticoid receptors (GR), might antagonize the observed effects. The direct competition of DHEA with corticosterone for GR would be expected to increase plasma corticosterone levels. Also, Kanik *et al*. (2000) reported a positive correlation between cortisol and serum DHEA level in healthy human subjects which in the same trend with our results in the general positive correlation between serum DHEA and corticosterone levels. In contrast, Svec and Porter (1998) suggested that the endogenous administration DHEA, by increasing the plasma DHEA/corticosterone ratio, is likely to suppress corticosterone levels by directly acting on the hypothalamic-pituitary-adrenal axis. Chang *et al*. (2003) suggested that DHEA acts directly on rat adrenal zona fasciculata-reticularis (ZFR) cells to diminish corticosterone secretion. Svec *et al*. (1995) results showed no effect on corticosterone level in obese rats administered DHEA for four weeks although its weight loss effect.

The CA is an antiandrogenic antiglucocorticoid synthetic hormone inhibiting the 3β hydroxysteroid dehydrogenase enzyme and induce a decrease in the DHEA, corticosterone and testosterone level in contrast with DHEA, its supplementation increases the level of

DHEA, corticosterone and testosterone. However, the effect of DHEA or CA on the brain monoamines was in the same trend, both the two drugs showing a significant elevation in hypothalamus monoamines especially serotonin and norepinephrine which are related with the hypolipidmic effect. In cortex monoamines related with satiety and meal termination. So, treatment with both DHEA+CA will be more effective in the hypolipidemic action. Treatment with the two drugs together will induce a normal level of DHEA, corticosterone and testosterone.

The production and metabolism of DHEA by hypothalamic astrocytes, the hormone, may be involved in the regulation of hypothalamic neuronal function as the astrocytes and neurons express 17α-hydroxylase/C17-20-lyase (P450c17) enzyme which is responsible for the conversion of pregnenolone to DHEA besides the capacity to metabolize DHEA into sex steroid hormones (Zwain and Yen, 1999).

Hull *et al*. (1999) reported that testosterone may increase dopamine release by up regulating nitric oxide synthase, which produces nitric oxide, which in turn increases dopamine release. Testosterone has been found to suppress dopamine turnover in the anterior hypothalamus of male rats (Simpkins *et al*., 1983). Also, perhaps testosterone promotes aggression by lowering serotonin levels (Charney, 2004). These results are in the same direction with those showing a negative correlation between the cortical monoamine neurotransmitters and DHEA level and positive correlation between DHEA and testosterone levels. Furthermore, it has been reported that DHEA administration stimulated the induction of the steroidogenic enzymes expressed in the skeletal muscle (Aizawa *et al*., 2007). As DHEA is considered one of the anabolic products used to improve weight and shape among adolescents through hindering lipogenic processes and improvement of protein deposition (Field *et al*., 2005). In young rats fed with high fat diet there was a positive correlation between DHEA and serum testosterone level $r = 0.72$, $p<0.001$, while a negative correlation $r = -0.42$, $p<0.001$ was found between serum DHEA and brain cortical content of dopamine. It has been found that testosterone suppresses dopamine turnover in male rats which was thought to be involved in androgen dependent aggression (Simpkins *et al*., 1983; Coccaro, 1996).

CONCLUSION

In spite of the proven anti-obesity properties of either DHEA or CA by direct effect on the hypothalamic monoamine neurotransmitters, several potential side effects may be drawn from the present study. The young rats fed on high fat diet were the most affected groups. So, young individuals should be aware of the unfavorable effects of DHEA when used as an over the counter supplementation. The drug may cause undesirable effects on development of aggressive behavior and may also affect the reproductive functions in young consumers in spite of its apparent anxiolytic effects.

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