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Influences of Hydrocortisone, DHEA, Estradiol and Testosterone on the Polyamine Metabolism of Mouse Brain, Kidney, Liver and Intestine

Sang-Hyun Choi, Boe-Gwun Chun*, Jong-Cheol Chun and Yeon-Sook Chun

Department of Pharmacology, Korea University College of Medicine, Seoul 136-075, Korea

ABSTRACT

The bilateral castration of male mice was operated under light ether anesthesia, and the sham operated mice were considered as the uncastrated. The treatments of mice with the following steroids were started one hour after operation.

Hydrocortisone 50 mg/kg (HC), dehydroepiandrosterone 250 mg/kg (DHEA), β-estradiol 5 mg/kg (E2), and testosterone 20mg/kg (TS) were subcutaneously injected into male ICR mice at noon for four days. Animals were sacrificed in the next-morning (at 10-12 A.M.) after the last injection.

The intestinal putrescine(PT) content was lower and the liver and intestinal spermine(SM) contents were higher in castrated mice(CM), comparing with those of uncastrated mice (UCM).

The intestinal PT content of UCM was markedly increased HC. But all brain polyamines of CM were significantly decreased by it. And HC also increased the spermidine(SD) content of kidney and liver and the intestinal PT content in CM.

E2 induced the marked increase of liver PT content with the moderate increase of renal SD in UCM. And E2 significantly increased the brain and liver PT contents and the all renal polyamine contents in CM.

Both of DHEA and TS induced the increase of renal PT content in UCM, and they also induced the marked increases of all renal polyamines of CM. In addition, TS increased the brain SM of CM.

These results suggest that the steroidal regulation mechanism of brain, kidney, liver, and intestine seems to be different from one another, and the renal activity of polyamine synthesis can be markedly enhanced by sex steroids.

Key Words: Polyamine metabolism, Diamine oxidase, Hydrocortisone, Estradiol, DHEA, Testosterone

Abbreviations: HC, hydrocortisone; E2, estradiol; DHEA, dehydroepiandrosterone; TS, testosterone; PT, putrescine; SD, spermidine; SM spermine; ODC, ornithine decarboxylase; SAM-DC, S-adenosylmethionine decarboxylase

INTRODUCTION

The di- and polyamines putrescine, spermidine, and spermine have been postulated to be essential for growth and differentiation and to be capable of interacting with many metabolic processes(Pegg and McCann, 1982; Pegg, 1986; Seiler, 1987).

There are many evidences supporting a role of them as second messengers in transmembrane signalling which favor Ca^{++} influx(Koenig *et al.*, 1988), cAMP degradation(Clo *et al.*, 1981), cGMP(Clo *et al.*, 1983) and diacylglycerol(DAG; Jadmar, 1977) formation, and a close mutual in-

* Correspondence Author

teraction between them and the other messengers such as cAMP(Russell and Haddox, 1979), IP_3(Mustelin *et al.*, 1986), DAG(Otani, 1985), or Ca^{++}(Caldarera *et al.*, 1986).

And it have been recently shown that the changes of the polyamine metabolism in most of organs might be thought essential in the hormonal regulations of their following functions such as hepatic regeneration(Byus *et al.*, 1977; Thrower and Ord, 1974; Russel and Haddok, 1979), hepatic drug metabolizing enzyme induction (Russel and Haddok, 1979); intestinal homeostasis(Karp *et al.*, 1987); pancreatic growth (Morisset and Benrezzak, 1984); cardiac development(Womble and Russell, 1983) and transmembrane signalling(Koenig *et al.*, 1988; Koenig *et al.*, 1989; Caldarera *et al.*, 1990); renal hypertrophy(Perin *et al.*, 1983) and tubular transport(Koenig *et al.*, 1983); adrenocortical steroidogenesis(Feige *et al.*, 1986); prostate(Rui and Purvis, 1987) and testicular Sertoli cells (Swift and Dias, 1987); developments of brain (Thomas and Schanberg, 1975) and behavior (Thomas and Schanberg, 1975; Butler *et al.*, 1978); axonal regeneration(Gilad, 1983); differentiation of lymphocytes(Otani et al., 1990), L6 myoblasts(Ewton, *et al.*, 1984), fibroblasts (Nissley *et al.*, 1976), bone and bone marrow (Rath and Reddi, 1981), chondrocytes(Takano *et al.*, 1983), neuroblastoma cells(Chen and Liu, 1983), or melanoma cells(Kapyaho and Janne, 1983; Bregman *et al.*, 1987); growth promotion of breast tumor(Manni *et al.*, 1989; Cohen *et al.*, 1988) and other tumors(Horn *et al.*, 1983; Slaga, 1984).

Several reports suggest that the ODC and/or SAM-DC activities were, after castration, decreased in most of organs(Rui *et al.*, 1987; Fjosne *et al.*, 1988), the castration effect was not affected by estradiol but prevented by dihydrotestosterone(Rui *et al.*, 1987).

And cortisol and thyroxine depressed ODC activity of the rat brain(Anderson and Schanberg, 1975).

In this study, therefore, the changes of polyamine metabolism induced by several steroid hormones were studied in normal and castrated male mice.

MATERIALS AND METHODS

Materials

Hydrocortisone acetate(HC), dehydroepiandrosterone(DHEA), estradiol cypionate(E2), and testosterone cypionate(TS) were purchased from Upjohn. Putrescine, spermidine, and spermine were purchased from Sigma. 1, 8-Diaminooctane, 4-fluoro-3-nitrobenzotrifluoride, dimethylsulfoxide, and 2-methylbutane were from Aldrich. Methanol and acetonitrile were HPLC-grade products of Merk. And other chemical were analytical grade. Male ICR mice, weighing 17-20 g, were supplied from Korea Experimental Animal Lab. Company.

Treatments of animals

Ten male mice were kept to a cage and allowed acclimated to a 12 hr light(7 AM to 7 PM) and 12 hr dark cycle for one week before being studied. The mice were subjected to bilateral castration at 11 A.M. under light diethyl ether anesthesia(Waynforth, 1980), and the sham-operated mice underwent similar surgical procedure. One hour after those procedures, mice were subcutaneously injected with HC 50 mg/kg or E2 5 mg/kg in cotton seed oil of 0.18% benzyl alcohol, and with DHEA 250 mg/kg or TS 20 mg/kg in cotton seed oil, once a day for 4 days. The mice were sacrificed in the next morning after the last injection for the analysis of tissue polyamine contents.

Polyamine HPLC analysis

Apparatus. The high performance liquid chromatography(HPLC) system was consisted of a Gilson HPLC pump, a Rheodyne 7125 injection valve, a ERC ODS-1161 column(3 um; 6 x 100 mm), a Knauer variable UV/VIS spectrometer, and a Linear dual-channel chart recorder.

HPLC analysis. The extraction process was done below 6°C according to that of Choi *et al.* (1989).

The 4-fluoro-3-nitrobenzotrifluoride(FNBT) derivatization of polyamines and the HPLC analysis condition were those originally described by Spragg and Hutchings(1983).

The N-2'-nitro-4' -trifluoromethylphenyl(NT-P) polyamine derivatives in the 20 ul of metha-

nol extract were quantitatively analyzed on a isocratic HPLC system equipped with an ODS column, using diaminooctane as an internal standard(Spragg and Hutchings, 1983; Choi *et al.*, 1989).

The recovery rates of NTP-polyamine derivatives were over 94.4%, and the calibration curves of them were consistently linear over a range of 50 picomole to 10 nanomole with the variations of less than 5% between identical samples, and the detection limit was less than 10 picomole on column with a S/N ratio of 5:1.

RESULTS

Effects of Steroids on the Brain Polyamine Contents

As shown in Fig. 1, the brain polyamine contents consisted predominantly of spermidine (SD: 260-370 nmole/wet g) and spermine(SM: 300- 420 nmole/wet g) with substantially lower

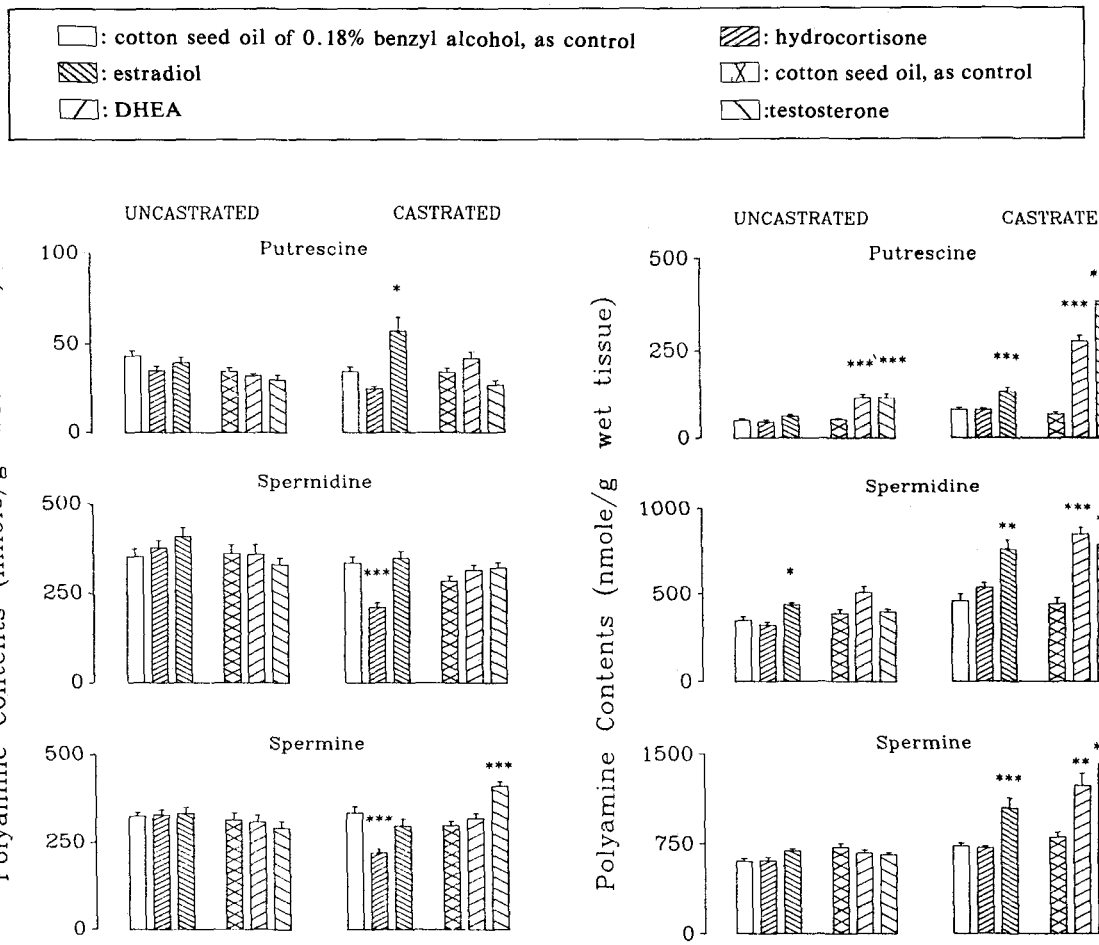

Fig. 1. Influences of hydrocortisone, estradiol, DHEA, and testosterone on the polyamine contents in the brain of castrated and uncastrated mice. Each column and bar represents the mean and standard error of 6 to 8 data. * and *** indicate $p<0.05$ and $p<0.01$ respectively.

Fig. 2. Influences of hydrocortiso-ne, estradiol, DHEA, and testosterone on the polyamine contents in the kidney of castrated and uncastrated mice. ** indicate $p<0.02$.

amount of putrescine(PT: 28-50 nmole/wet g), and all the contents were little changed 4 days after castration.

However, in the castrated mice, hydrocortisone 50 mg/kg(HC) induced the moderate decrease of PT content and the significant decreases of SD and SM contents, but estradiol 5 mg/kg(E2) caused the moderate increase of PT content and the slight decrease of SM content. Testosterone 20 mg/kg(TS) significantly raised up to 137.6% of the control SM value without any effect on PT and SD contents(Fig. 1).

Effects of Steroid on the Kidney Polyamine Contents

The renal PT, SD, and SM contents of uncastrated mice were 42-60 nmole/wet g, 540-790 nmole/wet g, and 300-430 nmole/wet g, respectively. Like to the brain contents, all the renal contents were not significantly changed after castration(Fig. 2).

However, in the uncastrated mice, E2 moderately increased all the polyamine contents, and dehydroepiandrosterone 250 mg/kg(DHEA) and TS significantly increased renal PT content. In the castrated mice, E2, DHEA, and TS caused the greatly meaningful increases of all the renal polyamines, comparing with their effects in the uncastrated(Fig. 2).

Effects of steroid on the hepatic polyamine contents

After castration, the PT content slightly increased and the SD rather increased slightly, but the SM content showed significant increase upto more than 142 %(Fig. 3). E2 markedly increased the hepatic putrescine contents of uncastrated and castrated mice upto 241.1 % and 245. 7 % of the control values, respectively(Fig. 3). TS and DHEA slightly increased hepatic PT

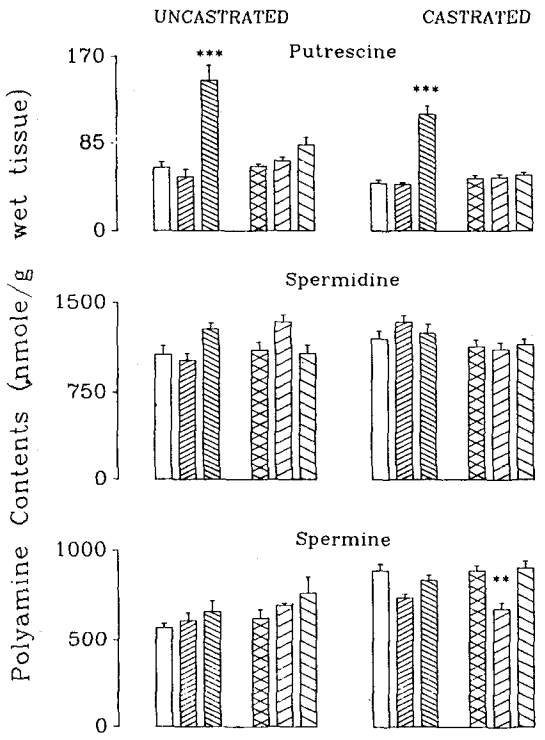

Fig. 3. Influences of hydrocortiso-ne, estradiol, DHEA, and testosterone on the polyamine contents in the liver of castrated and uncastrated mice.

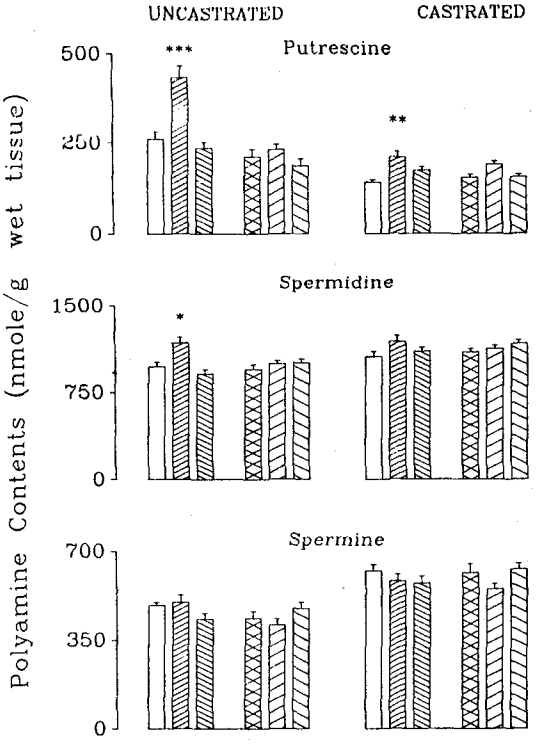

Fig. 4. Influences of hydrocortiso-ne, estradiol, DHEA, and testosterone on the polyamine contents in the intestine of castrated and uncastrated mice.

and SD contents of the uncastrated mice. And in the castrated mice, HC slightly decreased the SM content and DHEA significantly decreased it(Fig. 3).

Effects of steroid on the intestinal polyamine contents

After castration, like to the hepatic polyamine contents, the intestinal PT content significantly decreased, the SD content did not showed any significant change, but the SM content significantly increased, comparing with the values of uncastrated mice(Fig. 4). However, HC greatly increased the intestinal PT contents of uncastrated and castrated mice upto 167.1 % and 149.0 % of the control values, respectively. And the PT content of the castrated mice, unlike to that of the uncastrated, was slightly increased by E2 or DHEA(Fig. 4).

DISCUSSION

Several reports suggest that the ODC and/or SAM-DC activities were decreased in most of organs after castration(Rui *et al.*, 1987; Fjosne *et al.*, 1988), and the castration effect was not affected by E2 but prevented by DHEA(Rui *et al.*, 1987). And cortisol and thyroxine depressed ODC activity of the rat brain(Anderson and Schanberg, 1975), but Ientile *et al.*, (1988) reported that corticosterone and dexamethasone increased ODC and N^1-acetylspermidine transferase activities of the rat brain in a dose-dependent manner.

Recently, an our study(Choi *et al.*, 1990) showed that HC produced the markedly decreased activity of intestinal diamine oxidase and the significant increase of intestinal PT content, but the liver PT content was greatly increased by E2 but not changed by HC. Therefore, the present study was attempted to evaluate the influences of several representative steroids on the polyamine metabolism of brain, kidney, liver, and intestine in uncastrated and castrated male mice.

In this study, the brain polyamine contents of uncastrated mice were little changed by HC, E2 DHEA, or TS and HC produced the moderate decrease of PT content and the marked decreases of the SD and SM. But E2 moderately increased the PT content in brain of castrated mice, and TS moderately increased the SM content.

These results are in agreement with the data of Anderson and Schanberg(1975) but in contrast to the other(Ientile *et al.*, 1988). In any way, the inhibitory effect of HC on polyamine metabolism gives an important meaning, in consideration of the other previous reports demonstrating the age-related diminitions of ODC activity(Shain *et al.*, 1986; Rui and Purvis, 1987) and the glucocorticoid suppression of lesion-induced synaptogenesis(Scheff and Dekosky, 1989).

Meanwhile, in the uncastrated mice, the renal PT content was significantly increased by DHEA and TS, and the SD was moderately increased by E2. But the increasing effects of the steroids previously reported(Pegg *at al.*, 1982; Berger *et al.*, 1984; Sertich and Pegg, 1984) were markedly enhanced after castration, suggesting that one or more of the regulatory mechanisms such as catabolic activity(Seiler *et al.*, 1983), antizyme(Canellakis *et al.*, 1981; Tabor and Tabor, 1984), antizyme inhibitor(Fujita *et al.*, 1983), and ODC phosphorylation(Mitchell *et al.*, 1990) may be disturbed in the kidney after castration, or the kidney of castrated mice may be supersensitized to E2, DHEA, and TS(Shain *et al.*, 1986).

In this study, the liver polyamine contents were not affected by all steroids examined with the except of the marked increase of PT content induced by E2, as previously reported(Cohen *et al.*, 1970; Kaye *et al.*, 1971; Choi *et al.*, 1990).

By the way, the only PT content among intestinal polymines were, unlike to those of the liver, markedly increased by only HC but not affected by the other steroids.

The results obtained in the present study are consistent with previous papers of Choi *et al.* (1990) and other(Wing, 1988), demonstrating the organ specificities in the steroidal regulation of tissue polyamine metabolism.

But Karp *et al.* (1987) reported that HC increased intestinal activity of diamine oxidase, the major catabolic enzyme of polyamine, in contrast to that of Choi *et al.* (1990).

In summary, the present results are suggesting the organ specificities in the steroidal regulation of tissue polyamine metabolsm, i.e.; 1) in

castrated mice, the intestinal PT content may be lower and the SM contents of liver and intestine may be greater than those of uncastrated mice; 2) HC induces the marked increase of intestinal PT content but does not change the polyamine contents of brain, kidney, and liver, however, in castrated mice, HC significantly decreases the brain PT content; 3) E2 induced the marked increase of liver PT content with the moderate increase of renal SD in uncastrated mice, and E2 significantly increased the brain and liver PT content and all the renal polyamine contents in castrated mice; 4) both of DHEA and TS increased more greatly all the renal polymine contents of castrated mice than those of uncastrated mice, and particularly, TS increased the brain SM of castrated mice; 5) by the way, all the renal polyamine contents are, unlike to those of uncastrated mice, markedly increased by E2, DHEA, or TS.

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= 국문초록 =

Glucocorticoid 및 性 Steroid 홀몬에 의한 腦 및 腹部內 臟器의 Polyamine 代謝의 變動에 관한 硏究

고려대학교 의과대학 약리학교실

최상현 · 전보권 · 천종철 · 천연숙

웅성-마우스의 고환을 diethyl ether마취하에서 제거하고, 수종의 steroid 홀몬을 각각 매일 1회씩 4일간 피하주사한 다음 날의 오전 11-12 시에 뇌, 신장, 간장 및 소장의 polyamine을 검량하여 다음의 성적을 얻었다.

1. 고환절제-마우스(CM)에서, 소장 putrescine(PT)는 비고환절제-마우스(UCM)에 비하여 유의한 저하를 보였으나, 간 및 소장의 spermine(SM)은 오히려 유의하게 증가되었다.

2. Hydrocortisone 50 mg/kg는 UCM의 소장 PT는 현저히 증가시켰으나, CM의 뇌 PT 함량은 오히려 감소시켰다.

3. Estradiol 5 mg/kg는 UCM의 간 PT 함량을 현저히 증가시켰으며, CM에서는 간 PT 뿐만 아니라 신장의 전 polyamin 함량증가와 아울러, 다소의 뇌 및 소장 PT-증가를 유도하였다.

4. Dehydroepiandrosterone 250 mg/kg(DHEA)와 testosterone 5 mg/kg(TS)는 UCM의 경우 신장 PT 함량만 유의하게 증가시켰으나, CM에서는 신장의 PT, spermidine(SD), 및 SM 모두를 더욱 현저히 증가시켰고, 아울러 DHEA는 간 SM의 감소를, TS는 뇌 SM의 유의한 증가를 유도하였다.

이상의 결과로 미루어 볼때, 간 및 소장의 polyamine대사특히 PT함량의 변동은 각각 E2 및 HC에 의하여 보다 특이적으로 조절되고, 신장의 polyamine 대사는 성steroid들에 의하여 다소 비특이적인 조절을 받는 것으로 생각되며, 고환절제-마우스에서 나타나는 HC에 의한 뇌의 전 polyamine감소 및 성steroid들에 의한 신장의 전polyamine증가의 발현기전에 대한 연구가 있어야 할 것으로 사료된다.