SEX-DEPENDENT ACCELERATION OF THE METABOLISM OF METOPIRONE BY HYPOPHYSECTOMY IN THE RAT

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INTRODUCTION

In the previous paper[1], the present author reported a sex difference in the rate of metabolism of Metopirone [2-methyl-1,2-bis-(3-pyridyl)-1-propanone; Su-4885] in the rat and it was suggested that the difference in the level of ACTH might have some relationship with the difference in the rate of metabolism of Metopirone between male and female rats. In this study, a further evidence for the relationship of the low plasma ACTH level with the accelerated metabolism of Metopirone in the rat has been presented.

MATERIALS AND METHODS

Wistar rats of both sexes supplied from Animal Center Laboratory of Kyoto University aged 2–3 months after birth were used. Animals were maintained on a stock chow diet (CE-2, Japan Clea Co.) and given tap water for drinking *ad libitum* unless otherwise described.

Adrenalectomy and ovariectomy were performed by dorsal incision, orchiectomy was done by scrotal incision and hypophysectomy was done through the intra-aural approach[2]. All operations were performed one week prior to the following experiment and adrenalectomized rats and hypophysectomized rats were given 1% NaCl solution and 5% glucose solution to drink after operation, respectively.

Metopirone was administered perorally with a stomach tube in a dose of 100 mg/kg without anesthesia[1]. Blood was collected from abdominal aorta with a heparinized syringe 90 min after administration of Metopirone under Nembutal anesthesia (Sodium pentobarbital, Abbott Lab., 40 mg/kg, i.p.) and was centrifuged at 3,000 rpm for 15 min to obtain plasma, which was stored at −20°C until analyzed. After sacrifice, each rat was examined for the completeness of removal of the specified endocrine organ by visual inspection and the data from incompletely operated animals were discarded.

Chemical determination of Metopirone and its metabolites was done according to the method of Szeberenyi *et al.*[3] and the statistical evaluation of the difference between means

was done using the Student 't' test.

RESULTS AND DISCUSSION

Rats used in this experiment were still under development and their body weight increased by about 20% in males and by 14-20% in females during one week after operation in control, castrated and adrenalectomized groups. Only in hypophysectomized group, reduction in the body weight from that before operation was observed (about 8% reduction in both sexes).

In the control group, plasma levels of Metopirone were significantly higher in females than in males ($P<0.001$) (Table 1). This sex difference was known to be due to the rapid rate of reduction of Metopirone in male rats, as reported previously[1]. In the control group, plasma levels of the reduced substance of Metopirone were significantly higher in males than in females ($P<0.01$).

Marked acceleration of metabolism of Metopirone was observed in hypophysectomized female rats and their plasma levels of Metopirone approached near that observed in male controls. There were no significant differences between control and adrenalectomized or hypophysectomized male rats ($P<0.2$), although the mean levels of Metopirone were about two times higher in both groups than in control group. It has been reported that there is a sex difference in drug metabolizing enzyme activities in adult rats[4,5] and that adrenalectomy in male rats reduces the activities but not in female rats[5]. The elevated level of Metopirone found in some of the adrenalectomized male rats may be explained by these evidences. A longer interval after adrenalectomy might be necessary to exert a definite effect on the metabolism of Metopirone.

Kraulis *et al.*[6] reported that in the presence of ACTH, the metabolism of Metopirone was decreased *in vitro* and Kato and Gillette[5] found that the administration of ACTH to male rats decelerated the metabolism of aminopyrine and hexobarbital by liver microsomes. Although disturbances in many pituitary hormones besides ACTH must be considered to explain the effect of hypophysectomy in the present experiment, it can be postulated that in female rats, but not in males, the plasma level of ACTH is high enough to suppress the liver enzyme

Table. 1 Plasma levels of Metopirone and its reduced form 90 min after peroral administration in castrated, adrenalectomized and hypophysectomized rats.

	Male		Female	
	Metopirone μg/ml	Reduced form μg/ml	Metopirone μg/ml	Reduced form μg/ml
Control	3.6±1.3(11)	41.6± 8.3(11)	14.4±6.9(12)	30.0±10.0(12)
Castrated	4.8±1.3 (6)	45.4±14.6 (6)	16.4±7.9 (6)	42.3±19.4 (6)
Adrenalectomized	9.0±7.1 (5)	44.7± 6.8 (5)	16.7±4.0 (5)	32.0± 4.1 (5)
Hypophysectomized	9.0±6.4 (5)	70.7±37.3 (5)	5.9*±2.8 (7)	58.7±37.3 (6)

Values are Mean ±S. D. and numbers of animals are in parenthesis.
* denotes statistically significant difference from control ($P<0.01$)

activities to reduce Metopirone, considering the fact that the pituitary-adrenocortical activity is higher in female rats than in male rats[1,7].

Metopirone is a drug for assessment of pituitary reserve and is widely used. When pituitary reserve is small, a lower level of ACTH will accelerate the metabolism of Metopirone resulting in an abnormally smaller response to this drug and, therefore, it should be noted that results of Metopirone test may be altered variously by factors which affect metabolism of Metopirone[8].

SUMMARY

Effects of castration, adrenalectomy and hypophysectomy on the plasma levels of Metopirone and its reduced substance were examined after peroral administration in Wistar rats of both sexes. In hypophysectomized female rats, the plasma level of Metopirone was significantly lower than in controls. No definite effect of hypophysectomy was found in male rats. A possible relationship between plasma ACTH level and the metabolism of Metopirone was discussed.

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