Effects of Castration and Androgen on Glycosuria Appearance in the Diabetic KK Mice Induced by Monosodium Glutamate Administration

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(Received 19 February 1988/Accepted 17 June 1988)

Jpn. J. Vet. Sci. 50(5): 1121-1123, 1988

KEY WORDS: castration, diabetes, KK mouse.

KK mouse is one of the inbred strain established by Kondo *et al.* [6] from Japanese native mice. Many investigators have reported that the diabetic characters of KK mice resemble those observed in human maturity onset diabetes [4, 10, 11]. It has been reported that the chemical diabetes of KK mouse can progress to overt diabetes following obesity induced by feeding a high-caloric diet [7], introducing the yellow obese gene (Ay) [5], or hyperphagia induced by gold-thioglucose [8]. Monosodium glutamate (MSG) administration to neonatal mice has been reported by Olney [13] to cause destruction of the arcuate hypothalamic nuclei and give rise to syndrome of obesity. In KK mice administered with MSG, obese diabetes was induced at high percentage [1, 2]. These findings suggest that aging, dietary or other factors leading to obesity influence the incidence of diabetes in KK mice. On the other hand, considerable difference in sexes was observed in glycosuria appearance ratio in KK mice [12]. We observed disappearance of glycosuria after castration in the spontaneously diabetic KK mice. It is considered that sex hormones have great influence on glycosuria appearance in KK mice.

In the present paper, to clarify the role of sex hormone, especially androgen, in glycosuria appearance, castration and androgen administration were treated in obese diabetic KK mice induced by MSG.

Twenty two male KK mice maintained in our laboratory were used for this experiment. The mice were fed with a commercial pellet, CMF (Oriental Yeast Co.), ad libitum. All mice were administered subcutaneously with monosodium-L-glutamate (Wako Pure Chemical Industries) in a dose of 4 mg/g body weight one day after birth and weighed weekly after 3 weeks of age. Urine glucose was tested weekly by Tes Tape (Eli Lilly

Co., Indianapolis, IN) and that showed more than ++ (0.25%) was identified as positive. Glycosuria appeared in all mice at 8 weeks of age, continuing over 6 months of age. At 28 weeks of age, all mice were castrated under anaesthesia with ether. Fifteen diabetic KK mice were divided into three groups; A (control: non-operation, n=5), B (castrated, n=5) and C (castrated and testosterone administered, n=5). In group C, mice were injected subcutaneously everyday with testosterone propionate (Wako Pure Chemical Industries) in a dose of 100 to 200 μ g/head. Another seven diabetic KK mice were used for the experiment to examine the effect of adrenal androgen on glycosuria appearance. Dehydroepiandrosterone (DHA) was used as adrenal androgen. The castrated KK male mice were administered subcutaneously everyday with DHA (Wako Pure Chemical Industries) in a dose of 1000 μ g/head from the 10th day after castration.

Effects of castration and testosterone propionate on glycosuria appearance in the male diabetic KK mice are shown in Fig. 1. All mice in group A

Fig. 1. Effects of castration and testosterone propionate on glycosuria appearance in the male diabetic KK mice induced by MSG.

Arrow indicates: Subcutaneous administration of testosterone propionate.

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Table 1. Effects of castration and dehydroepiandrosterone* on glycosuria appearance in the male diabetic KK mice induced MSG

Treatment	Glycosuria appearance
	Glycosuric mice/mice examined (%)
Before castration	7/7 (100)
10 days after castration	0/7 (0)
10 days after administration of dehydroepiandrosterone	7/7 (100)

* Dehydroepiandrosterone was administered subcutaneously in a dose of 1000 μ g/head every day from the 10th day after castration.

continuously showed high concentration of glycosuria (+++; 0.5%) during this experimental period. In the mice in group B, appearance of glycosuria rapidly decreased, showing all negative on the 12th day after castration. In group C, glycosuria disappeared in 4 out of 5 diabetic mice on the 4th day after castration, but it appeared acutely after testosterone administration, and on the 24th day all mice showed high concentration of glycosuria again.

Effects of castration and DHA on glycosuria appearance in the male diabetic KK mice are shown in Table 1. In all mice, glycosuria disappeared on the 10th day after castration. DHA was administered to the mice from the 10th day after castration, glycosuria appearing again in all mice.

Obesity with aging was observed in most KK mice, however, spontaneous glycosuria was observed in about 30% of males and only 5 to 7% of females [12]. Although all the male and female KK mice administered with MSG in neonatal period showed considerable obesity, overt diabetes was observed in over 90% of the males and only 10 to 30% of the females. Considerable difference between sexes was detected in appearance ratio of glycosuria. Such difference has been also reported in rat [3] or cat [9]. Sex hormones take part in lipid metabolism. Androgen accelerates lipolysis and increases blood FFA levels, while estrogen accelerates lipogenesis and diminishes blood FFA levels, having an effect on blood glucose tolerance. In this experiment, it became pronounced that androgen had an important role in onset of obese diabetes. In adult male mice, very small percentage of blood androgen in

originated from adrenal androgen. However, in females, most of blood androgen is originated from adrenal androgen. Adrenal androgen is considered to play an important role in glycosuria appearance in female KK mice. It is considered that the role of estrogen in the mechanism of the obese diabetes should be examined further in KK mice. Moreover, effects of castration and androgen administration on changes of levels of other hormones including insulin need further investigation in KK mice.

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要 約

MSG で誘発した糖尿病 KK マウスの尿糖発現におよぼす去勢とアンドロゲンの影響 (短報): 野中 哲・樋口直子・新井敏郎・大木与志雄 (日本獣医畜産大学獣医生理化学教室)——KK マウスの新生子に Monosodium glutamate 4mg/g を背部皮下に単回投与した結果, 肥満性糖尿病が高率に誘発された. 糖尿病雄 KK マウスを 28 週齢で去勢した結果, 全例で尿糖が陰転した. 去勢後, testosterone あるいは副腎アンドロゲンを毎日連続投与するとそれぞれ尿糖が全例において再び発現した. KK マウスの糖尿病発現には性ホルモンとくにアンドロゲンが重要な役割を果たしていることが明らかとなった.