Gonadal hormone regulates the expression MATE1 and OCT2 in kidney tissue of type 2 diabetes mice (EP-376)

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Background and aims: Multi-drug and toxin extrusion 1 (MATE1) and Organic cation transporters 2 (OCT2) are important proteins of metformin transport and excretion in liver and kidney. Our previous study showed that there were gender difference of metformin's hypoglycemic effect and it was independently linked with the estrogen and testosterone levels in type 2 diabetes patients. This study was designed to observe the impact of estrogen and androgen on the renal expression of MATE1 and OCT2 in female and male db/db diabetic mice.

Materials and methods: Eight week-old db/db and their normal control mice were divided into hormone intervention group (n = 20) which were injected testosterone 10mg/Kg/d(n=10) or estradiol 1mg/Kg/d(n=10) for seven consecutive days, and control group (n = 10) received the same volume of olive oil for 7 days. Both the intervention group included male subgroup (n = 10) and female subgroup (n = 10), respectively, and also had normal control group (n= 5). The blood were collected to detect plasma testosterone or estradiol levels at day 7, the RNA and protein were extracted from kidney tissue to detect the expression of MATE1 protein and OCT2 mRNA and protein with Western Blot and Real-time PCR.

Results: (1) After treatment with exogenous hormones, plasma levels of estrogen (6.2±1.3 vs 5.0±0.94) and androgen (92±23 vs 64±9) increased markedly in both male and female mice(*P*<0.01,Table 1). (2) Renal OCT2 mRNA levels in testosterone-treated male(TM) and female(TF) mice were significantly higher than control female mice(CF, 2.6±3.78, *P*<0.05, Figure 1). On the contrary, treatment with estrogen in both of males(EM) and females (EF) had no significant impact on OCT2 mRNA expression(both *P*>0.05, Figure 1). Simultaneously, the MATE1 mRNA levels in testosterone- treated male group increased significantly compared to control male mice(CM, *P*<0.05) and estrogen–treated male mice (*P*<0.05, Figure 2). No obvious changes of MATE1 mRNA levels were found in both EM and EF(*P*>0.05, Figure 2). (3) The expression of OCT2 protein in TF was significantly higher than that of CF(*P*<0.05, Figure 3). However, the expression of both the MATE1 and OCT2 protein levels in TM group were higher markedly compared to CM(*P*<0.05 Figure 3,4). In estrogen-treated males, the MATE1 expression elevated significantly (*P*<0.05, Figure 4), but the OCT2 expression had no apparent change(*P*>0.05, Figure 3).

Figure 1 Comparison of OCT2 mRNA levels after exogenous sex hormone treatment in female(F) and male(M) db/db mice. A, Testosterone(TF) or estradiol treated(EF) female mice; B, Testosterone(TM) or estradiol treated(EM) male mice. *P<0.05, *vs* CM

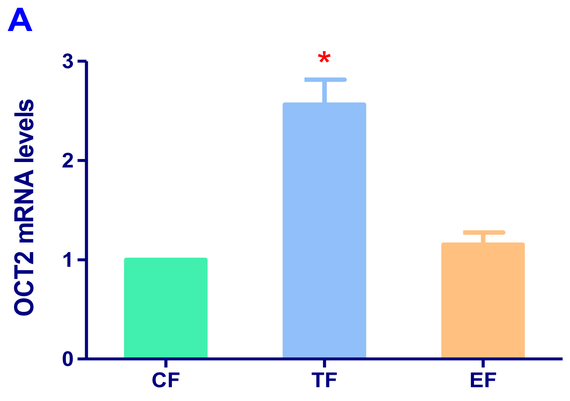


Figure 2. Comparison of MATE1 mRNA levels after exogenous sex hormone treatment in female(F) and male(M) db/db mice.
*P<0.05, *vs* CM; #P<0.05, *vs* EM

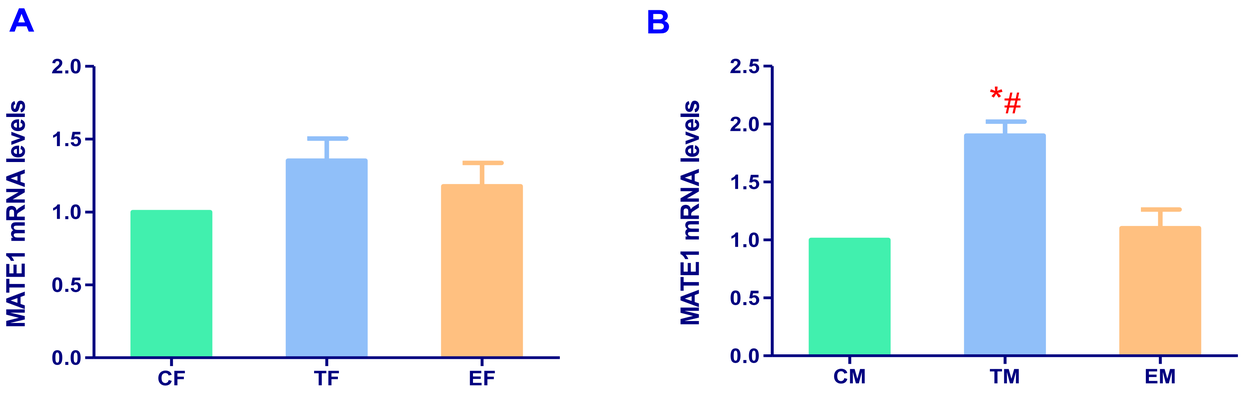
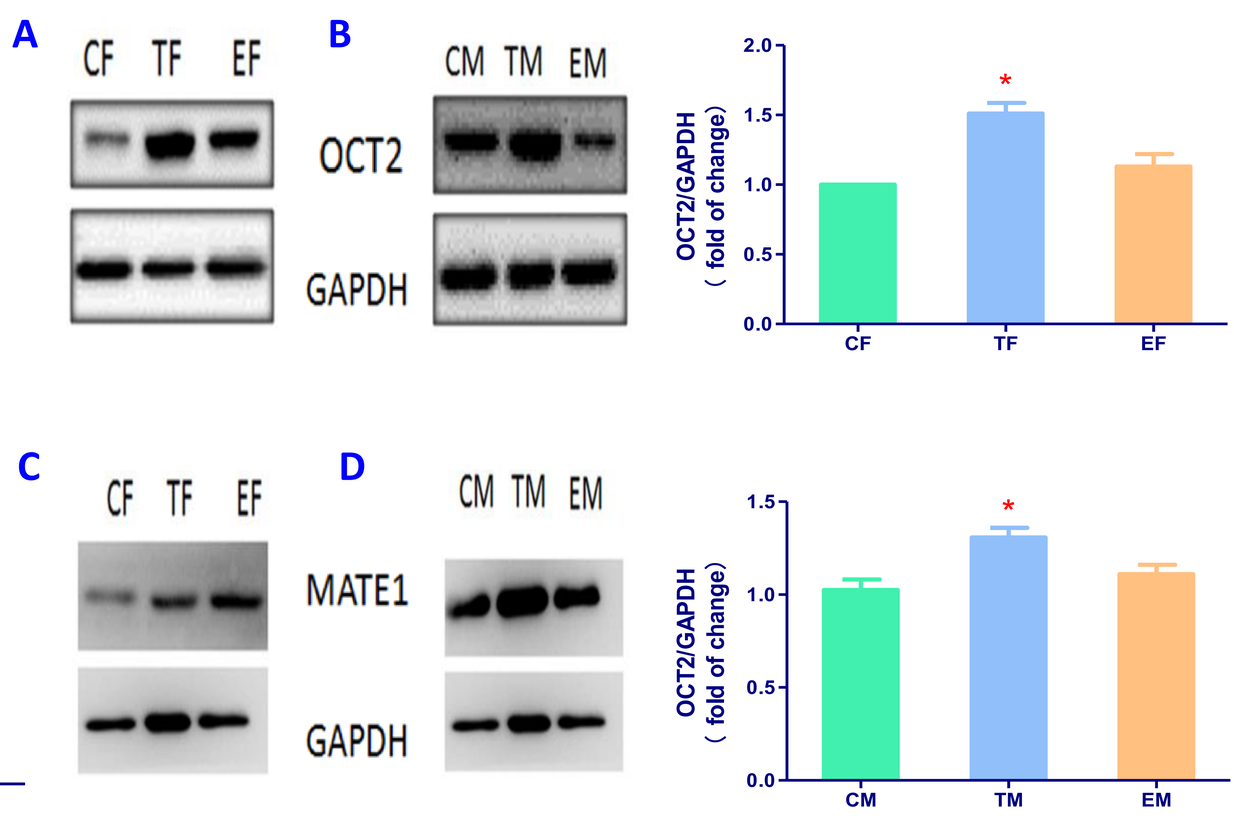


Table 1 Serum testosterone and estradiol levels in db/db diabetic and their control mice

	T(ng/ml)		E2(ng/ml)	
	Male	Female	Male	Female
Baseline	1.2±0.023	0.3±0.021	0.024±0.0013	0.51±0.0049
Control	0.61±0.091	0.51±0.1	0.072±0.0012	0.18±0.021
T-treated	92±23*	64±9*	0.38±0.12	0.42±0.18
E2-treated	0.58±0.081	1.5±0.48	5.0±0.94*	6.2±1.3*

Figure 3. Figure 18.Comparison of OCT2 and MATE1 protein expression after exogenous sex hormone treatment in female(F) and male(M) db/db mice. *P<0.05 vs control (CF or CM)



Conclusions: Estrogen and androgen up-regulate MATE1 expression of kidney in male diabetic mice, but have little effect on that of female mice; androgen increases OCT2 expression both in male and female mice, but estrogen has little effect on their OCT2 expression.

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Diabetes (to include obesity, pathophysiology & epidemiology)

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